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IMPROVING THE ASSESSMENT AND MANAGEMENT OF FISTULA-IN-ANO

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Abstract

Classical anal fistula surgery is both exploratory, to determine the extent of sepsis, and therapeutic. Imaging and novel surgical techniques have been employed to attempt to improve outcome, through sphincter conservation and by minimising relapse by detecting sepsis that might otherwise be missed at surgery.

The impact of MRI in recurrent fistula-in-ano was studied in 71 patients. MRI-guided surgery reduced further recurrence by 75%, and surgeons always acting on MRI had fewer further recurrences than those ignoring imaging ($p=0.008$). Even in primary fistula, MRI had a therapeutic impact of 10%, precipitating surgery likely to reduce recurrence in a small, though important, proportion of patients.

As surgery alone may be inaccurate, an outcome-derived reference standard was developed, allowing unbiased prospective comparison of preoperative fistula assessment. In 104 patients, anal endosonography (AES) was superior to digital examination. Whilst MRI was superior to both, AES provided accurate (91%) internal opening identification compared to MRI (97%), although MRI most accurately identified secondary extensions. A further study using three-dimensional AES found no benefit in extension localisation after hydrogen peroxide enhancement.

Although experts correctly interpreted more fistulas than novices using MRI, a short period of directed education rectified this difference, emphasising an important role for training. MRI helped delineate an important group of trans-sphincteric fistula with tracks extending cranially through the sphincter. The pathway of such tracks indicates

that sphincter division would need to be more extensive than suggested from the clinical localisation of the internal opening.

Extensive fistulotomy may jeopardise continence, and seton placement offers a simple alternative. However, the long-term success of the loose-seton technique was found to be lower than suggested by short-term follow-up. A prospective study used fibrin sealant in tracks that otherwise required long-term seton drainage. Overall, this technique failed in spite of early skin healing, which was predicted by MRI. Possible explanations of this were sought using an experimental porcine model of fistula-in-ano. Measurements of fistula volumes by stereology, and their signal intensity on MRI, both favoured sealant therapy compared to setons, suggesting that with modification, sealant therapy has a potential role in fistula treatment.

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Glossary

| | |
|-------------------|--|
| MRI | Magnetic resonance imaging |
| AES | Anal endosonography |
| EUA | Examination under anaesthetic |
| EAS | External anal sphincter |
| IAS | Internal anal sphincter |
| LM | Longitudinal muscle |
| 3D-AES | Three dimensional anal endosonography |
| HPE 3D-AES | Hydrogen peroxide enhanced 3D-AES |
| STIR | Short Tau Inversion recovery |
| DCEMRI | Dynamic contrast enhanced MRI |

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Statement of originality and contribution of author

The composition of this thesis has been entirely my work. It has not previously been submitted. Experimental and Clinical data were obtained between October 1998 and October 2002. Andrew Williams, Danillo Tarroni, Harriet Owen and Jared Torkington helped with clinical data acquisition. Experienced Consultant Radiologists and Surgical Research Fellows interpreted all imaging undertaken in clinical studies throughout this thesis, except when an inexperienced observer was being assessed (see Chapter 7). I collected all experimental data under the supervision of Dr Paul Sibbons, and received assistance in the preparation and assessment of specimens as alluded to in the acknowledgements.

My dissertation, *The therapeutic impact of magnetic resonance imaging in surgery for fistula-in-ano*, was accepted as partial fulfilment for the award of MSc in Surgical Science through the University of London in 2001. After further data acquisition, and extensive new statistical analyses, the project described in this dissertation has contributed towards studies presented in Chapters 3-5 in this present thesis.

Ethical Approval

Ethical committee approval had previously been granted for all studies contained within this thesis, as well as necessary exemption certificates from the Medicines Control Agency. For clinical studies, informed written consent was obtained from each patient. Patients were provided with a relevant patient information sheet. Patients were recruited via St. Mark's Hospital, except in the fibrin sealant study in chapter 10 where patients were also recruited from St. Mary's Hospital, London.

For experimental work, personal and project animal licences were granted by the Home Office after successful completion of courses approved by the Royal Veterinary College, and all aspects of the study, including animal husbandry were undertaken at Northwick Park Institute for Medical Research and Northwick Park and St. Mark's Hospital.

Dedicated to Lucy

**Thank you for your support
and patience**

Chapter 1:

Introduction, Hypothesis, Aims and Strategy

Introduction

Fistula-in-ano has a population incidence of approximately 1:10,000, and affects males in their working prime (Sainio, 1984). Most cases are idiopathic. Patients typically present with persistent perianal sepsis, and the natural history is such that few, if any, improve without surgical treatment. Anatomically, fistulas usually have a primary track, passing from an anal or rectal internal opening to an external opening, characteristically sited around the anal verge (Parks, Gordon, & Hardcastle, 1976). Additional secondary extensions may ramify from this primary track in various directions. Accurate assessment is necessary to ensure that all foci of infection are detected and eradicated during surgery, or recurrence is inevitable (Garcia-Aguilar et al. 1996).

Recurrent fistula-in-ano pose a difficult challenge, as scarring and distortion that accompany repeated surgery can further impair accurate clinical assessment. The result is that these patients become progressively harder to assess and treat. Even ostensibly simple primary fistula-in-ano may have extensions or internal openings that may be difficult to detect at initial surgery, but which may subsequently precipitate relapse (Sangwan et al. 1994). The key to breaking this loop is accurate initial preoperative assessment, the main aim of which is to identify unsuspected areas of sepsis so that they can be targeted for subsequent treatment. Traditionally, examination under anaesthetic (EUA) had been considered the most accurate way with which to assess fistula-in-ano. However, MRI has increasingly been shown to be more accurate than surgical assessment (Chapple et al. 2000; Lunniss et al. 1992) and thus might provide a worthwhile “roadmap” prior to operative assessment. Whether MRI-guided surgery improves outcome by preventing relapse, remains unanswered.

Endosonography can also characterise fistula-in-ano, however initial studies reported that this technique was no more accurate than digital assessment (Choen et al. 1991), and probably less accurate than MRI although there were no direct comparisons at that time (Lunniss et al. 1994). Following improvements in endoprobe technology and AES interpretation of fistula (Cho, 1999), together with the understanding that outcome needs to be taken into account when determining the reference standard used for assessment (Lunniss *et al.* 1994), the relative position of AES in preoperative assessment deserves reappraisal. Hydrogen peroxide instillation can enhance AES by acting as an ultrasound reflector (Kruskal, Kane, & Morrin 2001; Poen et al. 1998; Ratto et al. 2000; Sudol-Szopinska, *et al.* 2002) and some suggest this technique improves extension detection (Ratto, *et al.* 2000). However, existing studies have not adequately blinded observers and further research is required in this area to reduce bias. Whilst MRI may be an accurate means of assessing fistula-in-ano, it will only assist surgeons when correctly interpreted. Indeed, some authors describe difficulties interpreting MRI, and have suggested a learning curve is present and substantial (Scholefield et al. 1997). While this is unsurprising, it remains unclear whether directed education might facilitate improved MR interpretation for fistula-in-ano.

Sphincter division, or lay-open, may be curative though in high fistula can precipitate incontinence (Cavanaugh, Hyman, & Osler 2002), which is often accompanied by patient dissatisfaction (Garcia-Aguilar et al. 2000), therefore strategies to minimize its incidence are worthwhile. Whilst the internal opening level may be visualised at EUA, Park's classification suggests that trans-sphincteric fistulas track through the sphincter complex at right angles (Parks, Gordon, & Hardcastle, 1976). However, if these fistulas

ever tracked in a cranial direction through the sphincter from their internal opening, as is sometimes suggested clinically, these might be particularly hazardous to lay-open. A detailed reappraisal of the trans-sphincteric fistula is merited.

Sphincter conserving methods offer an alternative to lay-open. There has been recent interest in a novel therapy using fibrin sealant (Cintron et al. 1999). This technique needs further assessment, as where sealant fails it is unclear whether this is due to unfilled and thus untreated extensions. Furthermore, in cases where the overlying skin heals, it is important to determine whether the underlying track is ever eradicated. Additional sphincter conserving therapies include the loose-seton technique (Thomson & Ross 1989), which is successful in the short-term. However, long-term follow-up is warranted in order to appropriately counsel patients prior to seton removal. It is unfeasible to assess the histological effects of sphincter conserving treatments in human fistula-in-ano, although this might be possible using an experimental model in order to determine reasons for failure.

Therefore, this thesis aims to determine any effects of MRI-guided fistula surgery, the relative place of AES in preoperative fistula assessment and any benefits attained following hydrogen peroxide instillation. The role of education of observers interpreting MRI will be studied. Furthermore, the anatomy of the trans-sphincteric fistula will be re-appraised, together with both clinical and experimental analysis of sphincter conserving fistula therapies such as fibrin sealant and the loose seton-technique.

Hypothesis and Aims

1. MRI-guided surgery for recurrent fistula-in-ano improves outcome by detecting tracks and extensions that might otherwise go unrecognised at EUA.

Aim: To determine any effect on outcome of MRI-guided surgery for recurrent fistula-in-ano

2. Primary fistula may recur if incorrect assessment is undertaken at EUA. MRI guided surgery for primary fistula-in-ano may prevent relapse altogether.

Aim: To determine the therapeutic impact and any effect on outcome of MRI guided surgery for primary fistula-in-ano.

3. In the preoperative assessment of fistula-in-ano, digital examination is least accurate, and MRI most accurate, with AES intermediate

Aim: To prospectively evaluate the relative accuracy of digital examination, AES, and MRI for the pre-operative assessment of fistula-in-ano by comparison with an outcome-derived reference standard.

4. Hydrogen peroxide enhanced AES for fistula-in-ano is more accurate than unenhanced AES in extension detection.

Aim: To prospectively compare the accuracy of three-dimensional endoanal ultrasound to hydrogen peroxide enhanced three-dimensional endoanal ultrasound in recurrent or complex fistula-in-ano.

5. Experts more accurately classify fistula-in-ano using MRI than novices, however a period of directed education may improve inter-observer agreement.

Aim: To determine any difference in MRI interpretation of fistula-in-ano between an expert and a novice observer, and to assess inter- and intra-observer agreement after a period of directed education.

6. Trans-sphincteric fistula may cross the anal sphincter complex obliquely.

Aim: To prospectively determine the angle at which a trans-sphincteric fistula crosses the sphincter complex relative to the long axis of the anal canal.

7. Long-term outcome of the loose-seton technique as a sphincter-conserving treatment for complex fistula-*in-ano* is worse than described in the short-term.

Aim: To assess the long-term clinical result of the loose-seton technique at a minimum of 10 years after surgery.

8. Following fibrin sealant treatment of complex fistula-in-ano, MRI more accurately predicts outcome than clinical examination after skin healing.

Aim: To prospectively establish long-term healing of complex idiopathic anorectal fistula, without extension, after fibrin sealant treatment using clinical assessment and MRI to determine track healing.

9. Failure following fibrin sealant therapy for fistula-in-ano probably relates to inadequate track preparation.

Aim: To investigate the failure of fibrin sealant treatment for fistula-in-ano using an experimental porcine model, determining histological changes associated with sealant and setons.

Thesis Strategy

This thesis incorporates studies exploring: -

- The clinical role and value of anal fistula imaging
- The success of two sphincter conserving surgical techniques
- An experimental fistula model developed for novel surgical therapies.

A literature review presented in *Chapter 2* details fistula epidemiology, aetiology, classification, and methods of assessment. Traditional treatments and their effects on incontinence and recurrence rates are discussed. Whilst EUA has traditionally been used for fistula assessment, this approach alone can be misleading. Prospective studies assessing the effect of MRI-guided surgery on outcome in recurrent and primary fistula-in-ano are presented in *Chapters 3* and *4* respectively.

AES is a rapid and inexpensive alternative to MRI, however it was initially inaccurate compared to preoperative digital assessment of fistula-in-ano. *Chapter 5* presents a prospective study comparing the accuracy of pre-operative AES, MRI and clinical assessment of fistula-in-ano to an outcome-derived reference standard. *Chapter 6* presents a prospective blinded study comparing the accuracy of three-dimensional AES and hydrogen peroxide enhanced three-dimensional AES to a similar reference standard, thus determining whether hydrogen peroxide instillation improves extension detection using AES.

Pre-operative MRI of fistula-in-ano is becoming more common; however misinterpretation could negate its value. A prospective study determining any

differences in MRI interpretation between experts and novices, also assessing any effects of directed education, is presented in *Chapter 7*.

Whilst it has been previously suggested that most of the anal sphincter could be sacrificed during fistula surgery as long as the puborectalis was preserved (Milligan & Morgan 1934), it is apparent that functional disability is more common than previously realised. For this reason, sphincter-conserving techniques are advocated where function is likely to be compromised by lay-open, especially for certain trans-sphincteric fistulas. A prospective study presented in *Chapter 8* reappraises the anatomy of the trans-sphincteric fistula using MRI. Seton placement offers an alternative to fistulotomy, and whilst the loose-seton technique is sometimes advocated for complex fistula-in-ano, its long-term outcome is unknown. *Chapter 9* presents a review of traditional sphincter conserving fistula surgery, followed by a study of a cohort of patients who underwent loose-seton treatment some 10 years previously, in order to determine the long-term outcome of this technique.

Novel sphincter preserving techniques, including fibrin sealant treatment, have been developed for fistula-in-ano. However, late failure in some studies suggests persisting sepsis after skin healing, perhaps due to unfilled extensions following sealant instillation as a possible cause of recurrence. A literature review of fibrin sealant in *Chapter 10* is followed by a prospective study of fibrin sealant treatment in fistula-in-ano, which used MRI to exclude patients with extensions preoperatively and to predict outcome after early skin healing. Failure of sealant might also relate to inadequate primary track preparation. As it is unfeasible to assess track preparation and the histological effects of

sphincter conserving treatments, *Chapter 11* describes an experimental model developed for this purpose.

In summary, studies presented in this thesis are directed at improving fistula assessment and investigate novel sphincter conserving techniques. Each chapter details methodology pertinent to the particular study, except where this has been presented in preceding sections.

Chapter 2:
Background to the Work

Definition

Fistula is derived from the Latin term meaning a reed or pipe, and is applied to this perianal condition because the fistula track acts as a conduit for gas and secretions (Goodsall and Miles, 1982). Fistula-in-ano describes a track or cavity communicating with the rectum or anal canal by an identifiable internal opening. There is usually one external opening (Marks & Ritchie, 1977).

Historical

From ancient times, fistula-in-ano has been recognised as an important surgical condition, and there have been many writings on the subject. Hippocrates (fifth century B.C.), who detailed the relationship between fistula and abscess (Corman, 1980), wrote that timely drainage of an acute abscess might prevent it bursting into the rectum, and hence prevent fistula formation. Hippocrates also described internal rectal examination using a speculum, fistula probing, albeit using garlic stalks, and tight-seton treatment with horsehair.

The 14th century surgeon, John of Arderne, described a method of fistulotomy not dissimilar to that carried out today. Having threaded the track with a four-stranded ligature to prevent bleeding, he cut down onto a grooved director also inserted through the track whilst protecting the opposite wall of the anorectum with a shield inserted through the anus. John of Arderne observed that division of this main track was the most important means of facilitating cure. He felt, however, that fistula surgery was

troublesome and brought surgeons little credit, as patients were often unwilling to pay for treatment (Beynon & Carr, 1988).

This financial disparity was reversed in the 17th Century (Bodemer 1983), when Louis XIV of France developed acute perianal sepsis. The King, who was initially managed by the first physician, was prescribed several unsuccessful treatments, including a burning lead carbonate poultice application. Perianal abscess ensued and drainage was required on three occasions over a four-month period before fistula-in-ano was eventually diagnosed. After much debate Felix, first surgeon to the King, was summoned. While Felix was a skilled surgeon, he had not yet operated on a case of fistula. Surgery could occasionally be fatal at that time. Felix wisely studied all ancient writings, and after honing his skills on working class Parisians with the affliction, went on to surgically cure the King. Louis XIV displayed his gratitude by greatly elevating the position of surgery in France, and rewarding Felix with what is still believed to be the largest surgical fee in history, namely a large estate, elevation to the nobility and 300,000 French Francs.

In the 19th century Sir Frederick Salmon operated on Charles Dickens' fistula, which he attributed to too much sitting. While Dicken's felt it was a "cruel operation" (Bowen, 1956), he was so grateful that he helped Sir Frederick raise funds for the building of St. Mark's Hospital for Fistula and other Diseases of the Rectum, opened in 1835 (Granshaw, 1985).

Epidemiology

Scandinavian studies provide a population incidence of approximately 1:10,000 for the development of idiopathic fistula-in-ano (Ewerth et al. 1978; Sainio, 1984). Males are 1.5 to 7 times more likely to develop fistula-in-ano compared with females, depending on the population studied (Misra & Kapur 1988; Sainio, 1984). Lunniss et al (1995a) suspected that altered sex hormones may contribute to these gender differences, as no significant difference in anal glands had previously been noted between the sexes in earlier work (McColl, 1967). However, Lunniss found no evidence of androgenisation in female patients compared to controls, instead suggesting that an increased ability of anal glands to convert androgen might be important.

The peak incidence for fistula is in the fourth decade (Sainio & Husa, 1985b), with most occurring between the ages of 20 and 60. Patients with perianal abscesses, the acute precursor, demonstrate a similar age distribution though often present a year or two earlier (Schouten & van Vroonhoven, 1991). Indeed, fistulas are extremely rare in childhood (Hill, 1967), and almost never seen in young girls (Fitzgerald, Harding, & Ryan 1985). As most fistulas in children occur below the age of two years, some authors have suggested a hereditary aetiology (Poenaru & Yazbeck 1993). Indeed Parks (1961) suggests a congenital abnormality in the anal glands predisposing to infection. Some suggest that fistulas or abscesses recurring after childhood indicate an underlying cause such as Crohn's disease (MacDonald, Wilson-Storey, & Munro 2003).

No specific racial differences have been identified for developing fistula-in-ano. In a report from Nigeria, the age and sex distribution of patients with fistula was similar to that in western studies (Akinola & Hamed 1989). Whilst Hippocrates suggested that

fistula may result from riding or rowing (Corman, 1980), sedentary occupation or lifestyle has not subsequently been noted to be associated with fistula in large population based studies (Sainio, 1984). Eisenhammer (1964) hypothesised that infective diarrhoea may contribute to fistula pathogenesis, however there is no supportive data.

Aetiology

Over 90% of fistula-in-ano are so called non-specific or cryptoglandular, and studies undertaken in this thesis mainly pertain to this group. The differential diagnosis includes fistula associated with other conditions such as: -

- Crohn's disease
- Tuberculosis
- Hidradenitis suppurativa
- Pelvic diverticular disease
- Carcinoma
- Actinomycosis
- Trauma
- Foreign bodies (Lockhart-Mummery, 1929)

These less common causes are briefly considered below. Other conditions such as rectovaginal fistula (Mazier, Senagore, & Schiesel 1995; Watson & Phillips 1995), rectourethral fistula and pilonidal sinus which can occasionally mimic fistula-in-ano (Taylor, Halligan, & Bartram 2003), are not discussed.

Fistula-in-ano is a common presenting feature of Crohn's disease. Lockhart-Mummery (1975b) reported that approximately 61% of patients with Crohn's have an anal lesion, of which many were fistula-in-ano. Standard surgical techniques, including fistulotomy, can be used in Crohn's fistula and effect cure (Sohn, Korelitz, & Weinstein 1980), however the course and nature of Crohn's fistula is often more protracted, so that 20% eventually require proctectomy (Bell et al. 2003b). A more pragmatic approach is often taken in Crohn's fistula, aiming to cut down the number of acute septic episodes through loose-seton drainage (Scott & Northover 1996).

Hidradenitis presents in a similar demographic group to fistula, and may coexist whereby the fistula is usually superficial (Culp, 1983). Anal tuberculosis is rare, however Shukla *et al.* (1988) proposed that in those parts of the world where tuberculosis is prominent, the fistula should be examined histologically, especially where it is complex or there are other manifestations of the disease, as 15% may then be tuberculous in origin. Actinomycosis, which is characterised by the appearance of small yellow "Sulphur" like particles, can cause perianal sepsis. This condition requires combined medical and surgical intervention (Fry, Birnbaum, & Lacey 1992).

Whilst anal or rectal cancer may fistulate, it is rare that carcinoma develops in a fistula (Jensen et al. 1988). Furthermore, fistula-in-ano associated with developmental abnormalities such as presacral dermoids or rectal duplication cysts are extremely rare (La Quaglia et al. 1990). Perineal fistula may have no anal disease though may result from intra-abdominal conditions, such as sigmoid diverticular disease or small intestinal fistula (Parks & Gordon 1976).

Non-specific or Cryptoglandular fistula

The cryptoglandular theory is now widely accepted for the pathogenesis of fistula-in-ano. To understand fistula pathogenesis and accurately classify fistula, one must understand the relevant anal canal anatomy together with the relationship of the anal glands and their central role in fistula-in-ano. These aspects will be considered below.

Anal Anatomy

The anal canal commences as the rectum passes posteriorly and caudally through levator ani (Walls, 1983). It is approximately 5cm long in adults (shorter in females) when measured from the puborectalis muscle to the anal verge (Williams et al. 2001). The anal sphincter musculature, which helps hold the anus closed except to allow passage of faeces or flatus, has been considered as a “tube within a funnel” (Parks, 1961). The levator ani and external anal sphincter (EAS), both composed of striated muscle, form the upper sides and stem of this outer “funnel” respectively. The inner “tube” is composed of smooth internal anal sphincter (IAS) and longitudinal muscle (LM) fibres. This basic structure is outlined in Figure 1 (page 33).

The Pelvic Floor

The levator ani (coccygeus, iliococcygeus and pubococcygeus) forms the pelvic floor, and is attached to the pubis anteriorly, the coccyx posteriorly and the white line which traverses the fascia overlying obturator internus laterally. The puborectalis, formed from the anterior fibres of the pubococcygeus, forms a sling pulling the rectum forward. The

coccygeus muscle fibres decussate between the coccyx and the anal canal to form the ano-coccygeal raphe (Oh & Kark, 1972).

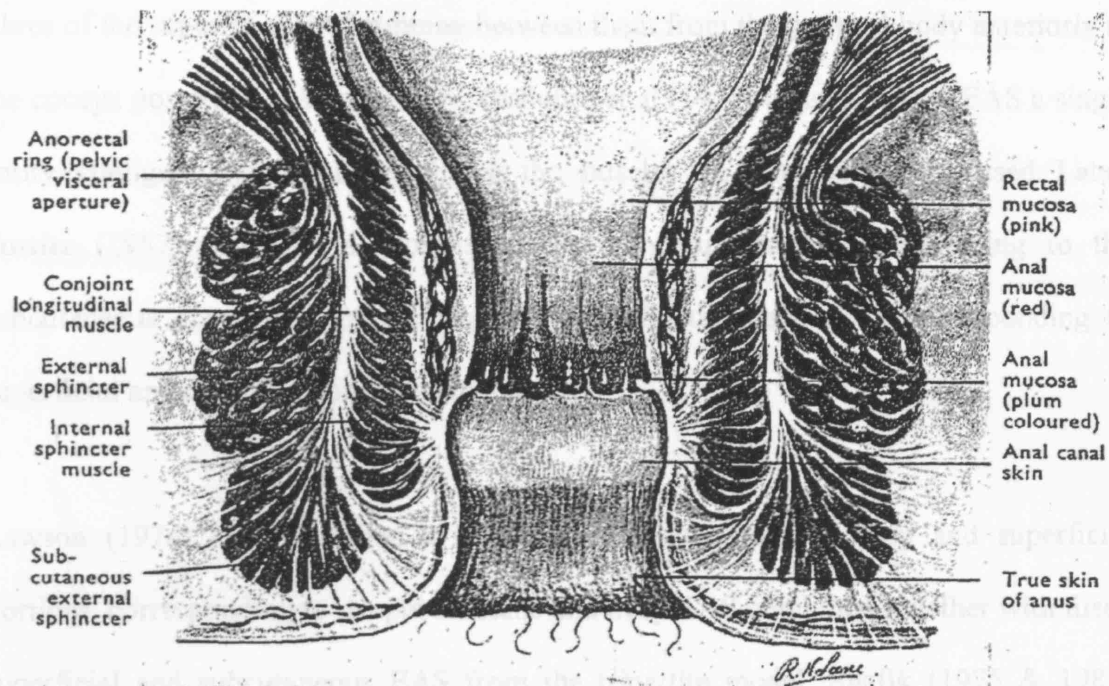


Figure 1: The linings of the anal canal and the anal musculature

(Copyright. The Royal College of Surgeons of England. Reproduced with permission). From Morgan CN & Thompson HR 1956 Surgical anatomy of the anal canal with special reference to the surgical importance of the internal sphincter and conjoint longitudinal muscle. *Ann.R.Coll.Surg.Engl.* 19: 88-114.

The Puborectalis and the External Anal Sphincter

The EAS lies in continuity with puborectalis proximally, at least posteriorly in both sexes, merging distally with the perianal skin. The intersphincteric space lies medial and the ischiorectal fossa lateral to the EAS, which surrounds the LM. In females the EAS is shorter anteriorly than in males (Gold *et al*, 1999) and forms a greater proportion of anal canal length, which has important implications for fistula surgery.

The most classical description of the EAS is of a tripartite structure (Milligan & Morgan, 1934) with deep, superficial and subcutaneous portions. The deep and subcutaneous sphincter form rings of muscle unconnected to the coccyx, with elliptical fibres of the superficial EAS running between them from the perineal body anteriorly to the coccyx posteriorly. Alternatively, Goligher et al (1955) considered the EAS a single entity, contiguous with puborectalis, as the muscles are macroscopically fused. Later, Fowler (1957) proposed a bipartite EAS, with superficial, corresponding to the subcutaneous component of the tripartite classification, and deep corresponding to superficial and deep components combined.

Lawson (1974) also described a bipartite EAS consisting of deep and superficial portions, corresponding to the puborectalis and deep EAS combined together with fused superficial and subcutaneous EAS from the tripartite model. Shafik (1975 & 1987) proposed a triple-loop description of anal sphincter anatomy, attempting to provide a new concept that, the rectum extended down to the perianal skin (Shafik, 1982). The top loop included puborectalis and the deep EAS; the intermediate loop was equivalent to the superficial EAS and the base loop was equivalent to the subcutaneous EAS, which attached to the perianal skin. Shafik also maintained that the puborectalis was part of the EAS.

More recently, Fucini et al (1999) used a nerve stimulator during fistula surgery to identify striated muscle components. A layer of connective tissue was found in all cases where the striated muscle was well preserved, extending from the intersphincteric space to the ischiorectal fossa. Furthermore, there seemed to be a plane of separation between the puborectalis and the main body of the subcutaneous EAS, with the angle this

subtended to the sagittal plane different in each case. They believed this connective tissue plane was the only high pathway for sepsis to track to the ischiorectal fossa. Furthermore, they could not demonstrate a distinct deep EAS. Fucini et al also suggested that many fistulas appearing to loop upwards were erroneously classified as suprasphincteric as puborectalis usually lay cranial to the track. Garavoglia et al (1993) had previously found the deep EAS and puborectalis inseparable in a proportion of patients. Obviously, discrepancy still exists about the exact structure of these muscles, however the importance of spread of sepsis to the ischiorectal fossa needs further evaluation.

The Longitudinal Muscle

The LM, lying medial to the EAS and lateral to the IAS in the inter-sphincteric space, is a continuation of the longitudinal smooth muscle of the rectal wall, augmented with striated muscle from several sources including puborectalis (Milligan & Morgan, 1934) and EAS (Shafik, 1976). LM fibres penetrate the IAS adding to the subepithelial tissue, and also traverse the EAS forming septa, which insert into the lower anal canal skin and adjacent perineum, also termed the corrugator cutis ani muscle. As such, the LM binds the sphincter mechanism and anal canal together (Lunniss & Phillips 1992). It may have a role in continence, also helping evert the anus during defecation (Shafik, 1976). Some believe that surgical procedures stretching or transecting the sphincters cause functional changes by their action on this element of perianal connective tissue (Haas & Fox, Jr. 1977). Whilst extensions into the intersphincteric plane probably help contain sepsis and anchor the IAS and subepithelial tissues, those through the EAS, are often implicated in the pathways of spread of fistula-in-ano (Lunniss & Phillips, 1992). It is the

arrangement of these outward extensions where most controversy exists, due to differences regarding the EAS structure. Abel (1932) felt two columns of LM divided the EAS, whilst Milligan and Morgan (1934) described two septa splitting the EAS according to its tripartite nomenclature. Parks (1954) described multiple septa in the lower anal canal, effectively fanning the subcutaneous EAS.

The Internal Anal Sphincter and Subepithelium

The IAS, lying medial to the LM and lateral to the subepithelial layer (Figure 1. Page 33), is a thickened continuation of the circular smooth muscle of the rectum. It usually terminates before the end of the subcutaneous EAS (Morgan & Thompson, 1956) and is between 2mm-4mm thick, increasing in thickness with age.

Between the IAS and EAS, lies the intersphincteric plane. The subepithelial tissue, which contains connective tissue and the muscularis submucosae ani (Walls, 1983), forms the basis of the vascular cushions (Parks, 1956) which help maintain a watertight sphincter mechanism. Three major cushions are found: right anterior, right posterior and left lateral, which when enlarged are responsible for haemorrhoids.

Epithelium

In the upper anal canal are longitudinal ridges, the columns of Morgagni. The lower ends of adjacent anal columns are joined together by small horizontal pockets, where the anal valves are situated. The rectum is lined by columnar epithelium, which extends caudally to the anal valves or dentate (pectinate) line, representing the endoderm:

ectoderm junction. Below this, the anal canal is lined by keratinised stratified squamous epithelium as far as the lower border of the internal sphincter. Whilst the dentate line effectively marks an altered type of mucosa, there is usually a variable level transition zone, known as the pecten, where mucosa gradually changes from one type to another (Parks, 1961). Below the pecten is normal skin. At this junction lie large apocrine and sweat glands, thought to lubricate defecation (McColl, 1967). These glands are thought to be responsible for a large proportion of acute perianal abscesses where no anal canal internal opening is found (Grace, Harper, & Thompson, 1982).

Anatomical Spaces

The intersphincteric space extends superiorly to the level of puborectalis. The supralelevator or pararectal space lies above this point, bounded medially by the lateral wall of the rectum and laterally by the sloping levator ani muscle. The ischiorectal fossa lies lateral and infero-lateral to the EAS and levator ani muscles respectively. It is bounded in its lateral aspect by the obturator internus (Figure 2, page 38).

Superficial spaces are also described (Lilius, 1968). The submucous space extends superiorly from the dentate line below the mucosa, and lies medial to the internal sphincter. The marginal space immediately underneath the skin contains the external haemorrhoidal plexus, and is bounded laterally by the IAS and LM fibres attached to the skin. It extends superiorly to the attachment of the mucosal suspensory ligament at the level of the anal sinuses. The perianal space lies lateral to the marginal space, separated from the ischiorectal fossa by fascia derived from both the gluteal region and the longitudinal muscle.

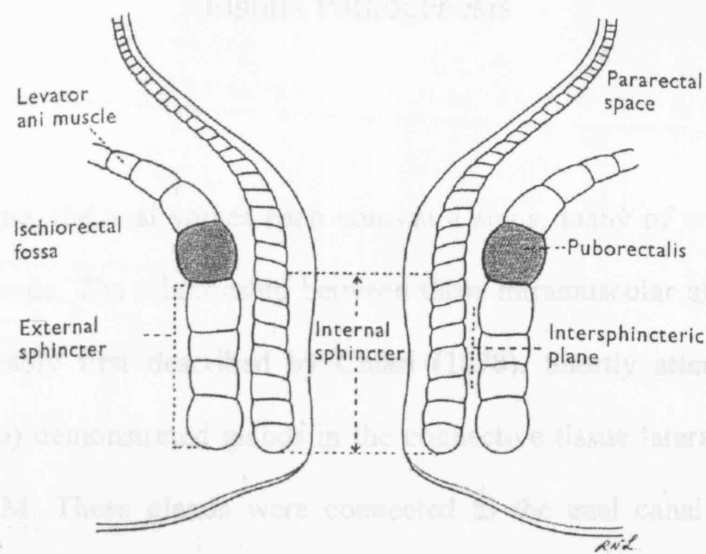


Figure 2: Coronal section of the pelvic floor and spaces

The longitudinal layer of the rectal wall and anal canal is omitted for the sake of simplification.

(Parks AG, Gordon PH & Hardcastle JD 1976 A classification of fistula-in-ano. *Br.J.Surg.*63: 1-12. ©British Journal of Surgery Society Ltd. Reproduced with permission; granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

Fistula Pathogenesis

Anal Glands

At the dentate line, the anal valves each conceal a sinus, many of which lead to anal intramuscular glands. The relationship between these intramuscular glands and fistula-in-ano was probably first described by Chiari (1878). Shortly after, Herrmann and Desfossess (1880) demonstrated glands in the connective tissue lateral to the IAS and medial to the LM. These glands were connected to the anal canal lumen by ducts crossing the IAS. Anal ducts are 2-8mm in length (Parks & Morson, 1962) and usually lined by stratified columnar epithelium. Johnson (1914) found 6-8 glands in each anorectum, also noticing ducts tracking caudally and laterally through the subepithelium to pierce the IAS, where they ramified, occasionally reaching the longitudinal layer. Johnson also noticed anal submucosal glands at this level. Whilst Hill *et al* (1943) only noticed glands penetrating the IAS in 2 out of 17 cases, McColl (1967) noted glands penetrating right through the IAS (Figure 3, page 40) in almost 50%. Some even report glands lateral to the EAS (Lockhart-Mummery, 1929). McColl also noted between 4 and 16 processes per duct, and hypothesised that patients with multiple processes and mucous secreting glands were predisposed to fistula-in-ano.

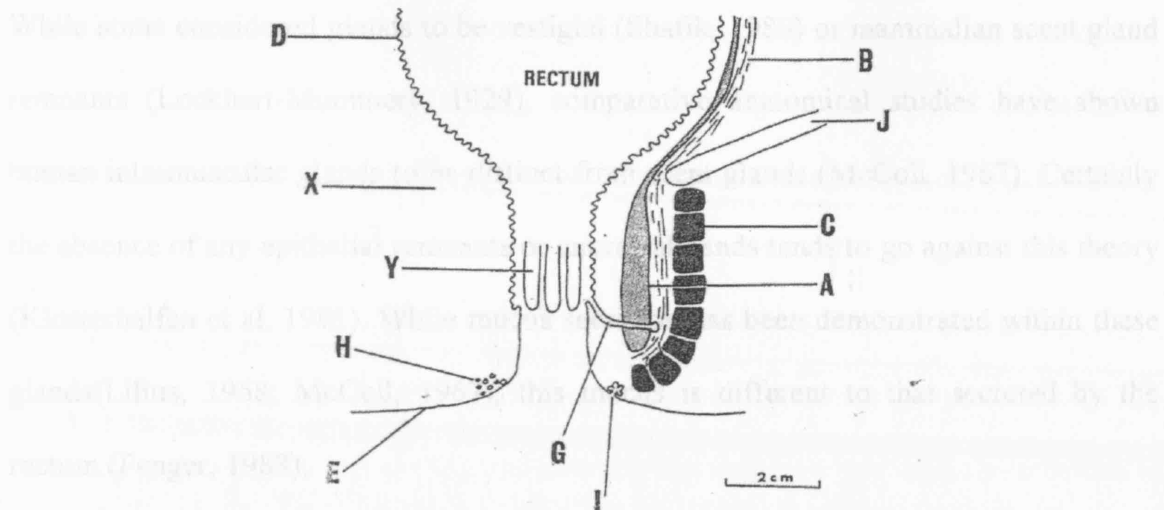


Figure 3: Diagram of anal canal demonstrating glands

Coronal section of adult anal canal illustrating anatomy. Internal sphincter (A), Longitudinal layer (B), external sphincter (C), rectal mucosa (D), perianal skin (E), anal gland (G), extending down from a crypt through submucosa and internal sphincter, apocrine glands (H), sebaceous glands (I), levator ani (J), site of anorectal ring (X), columns of Morgagni (Y) at the lower border of which are the valves of Ball (or pectinate line).

(Copyright. The Royal College of Surgeons of England. Reproduced with permission) From McColl, I. 1967 The comparative anatomy and pathology of anal glands. Arris and Gale lecture delivered at the Royal College of Surgeons of England on 25th February 1965. *Ann.R.Coll.Surg.Engl.* **40**: 36-67.

Histoanatomical study in adults has shown the majority of glands at dentate line level, with only a fraction penetrating the EAS (Seow-Choen & Ho, 1994), however others report glands situated just caudal or cranial to the dentate line (Eisenhammer 1978; Hill, Shryock, & Rebell, 1943). Furthermore, glands can occasionally communicate with ducts and the anal lumen above the level of the anal sinuses (Walls, 1958). Whilst some studies report intramuscular glands more frequently situated in the posterior aspect of the anus (Parks & Morson, 1962), other larger series have found them more evenly distributed.

While some considered glands to be vestigial (Shafik, 1980) or mammalian scent gland remnants (Lockhart-Mummery, 1929), comparative anatomical studies have shown human intramuscular glands to be distinct from scent glands (McColl, 1967). Certainly the absence of any epithelial remnants or anorectal bands tends to go against this theory (Klosterhalfen et al. 1991). While mucus secretion has been demonstrated within these glands (Lilius, 1968; McColl, 1967), this mucus is different to that secreted by the rectum (Fenger, 1988).

Cryptoglandular Hypothesis

Lockhart-Mummery (1929) proposed that anal glands provided a pathway for infecting bowel organisms to cause perirectal abscesses. Tucker and Hellwig (1933) substantiated this work, confirming that anal sepsis originated in ducts, rather than in the crypts as some had thought at that time.

Eisenhammer (1958), in his *Cryptoglandular hypothesis*, recognised the central role of glands in the pathogenesis of fistula-in-ano. Eisenhammer based his observations on the high intermuscular abscess, believing that most fistula-in-ano resulted from intermuscular gland infection. He believed the IAS impenetrable to sepsis, as he had never seen evidence of deep infection following severe superficial necrosis, as could happen after haemorrhoidal injection sclerotherapy, believing the weak point in the IAS lay at the anal valves, where ducts connect with deep intermuscular space glands. Eisenhammer recognised that anal glands were largely situated in the intersphincteric space and represented the seat of infection. The internal opening of an anal fistula was almost always at dentate line level where the valves lay in the crypts. Eisenhammer

believed fistula and abscess to be part of the same process, and that fistula was caused either by spontaneous abscess drainage or incorrect surgical drainage of an abscess to create a fistula and expressed the importance of internal anal sphincterotomy for fistula-in-ano.

Parks (1961) recognised that fistula could spread in several directions from an initiating infecting gland (Figure 4, page 42), and also felt that infection was unlikely to be due to faecal contamination, as almost 50% of fistulas had no clinically detectable internal opening. Park's examined histological specimens, and found between 6-10 glands around each anal circumference. In many cases, fistulas were associated with cystic dilatation of glands, often related to an obstructed duct. Park's believed this dilatation a necessary precursor to fistula development.

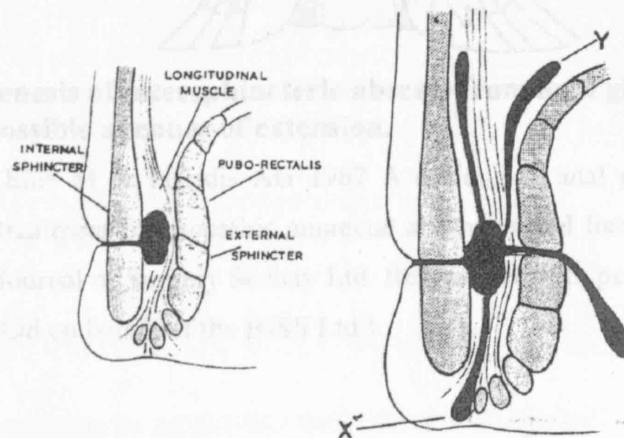


Figure 4: Diagram to illustrate the spread of infection from the primary anal gland abscess into the surrounding tissues.

The primary anal gland abscess is on the left and the surrounding tissues to the right. The commonest course is that marked X, the most rare Y.

Parks AG. 1961 Pathogenesis and treatment of fistula-in-ano. *BMJ* 1: 463-469. (Reproduced with permission from the BMJ Publishing Group)

Alternatively, Shafik (1979 a & b) postulated that anorectal sepsis results from central space infection. He described this space as a circumferential space in the lower perianal region, bounded superiorly by the LM termination, and inferiorly by the lowermost loop of the EAS. He thought that the central LM tendon within this space contained anal glands, which became the seat of sepsis that tracked following breaches in anal mucosa. He also believed that infection spread to surrounding areas via longitudinal fibres, and was exacerbated by straining during defecation. Others do not document these thoughts.

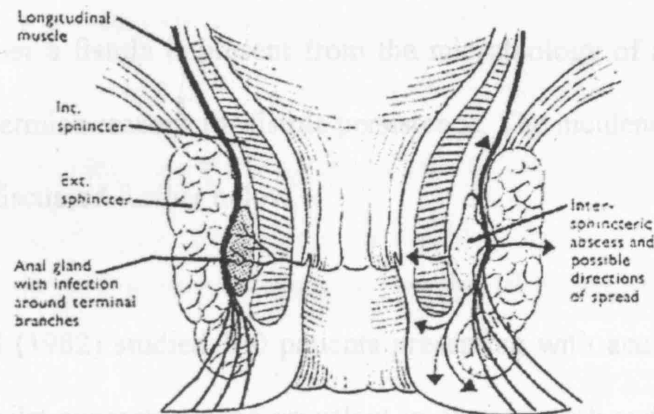


Figure 5: The genesis of intersphincteric abscess from anal glandular infection, and possible avenues of extension.

(Goligher JC, Ellis M & Pissidis AG 1967 A critique of anal glandular infection in the aetiology and treatment of idiopathic anorectal abscesses and fistulas. *Br. J. Surg.* **54**: 977-983. ©British Journal of Surgery Society Ltd. Reproduced with permission; granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

Whilst controversy remains over fistula pathogenesis, most accept the cryptoglandular hypothesis. As most anal glands occur in the intersphincteric space it seems plausible that sepsis may track from here along the line of least resistance in the longitudinal muscle (Goligher, Ellis, & Pissidis 1967) (Figure 5, page 43). The importance of glands lateral to this space is presently unknown (Morgan & Thompson, 1956).

Golligher (1967) believed that cryptoglandular infection led to a proportion of fistulas, and whilst many fistulas can be explained by this hypothesis, those described as extrasphincteric are likely to be due to other conditions such as trauma (Seow, Leong, & Goh, 1991), or inflammation caused by Crohn's or diverticulitis. Furthermore, those occurring at the anal verge are likely to relate to apocrine gland infection.

Microbiological Aspects

Interest in organisms cultured from fistula-in-ano developed for several reasons. Firstly, to predict whether a fistula is present from the microbiology of an acute abscess, and secondly, to determine reasons for fistula persistence. The incidence of fistula following acute sepsis is discussed further below.

Whitehead et al (1982) studied 140 patients presenting with acute perianal sepsis and reported that whilst anaerobes were prevalent in patients with and without fistulas, Gut and Gut specific organisms, including *Bacteroides*, were more predictive of fistula. Interestingly, skin organisms did not predict a fistula.

At a similar time, Grace et al (1982) reported on 125 patients with acute anorectal sepsis. In that study, the surgical team were blinded to culture reports. Two-year follow-up was obtained in the majority. Of 34 patients culturing skin-derived organisms after abscess drainage, none subsequently developed a fistula. However 62 of 68 patients with a fistula cultured bowel derived organisms. They concluded that where no fistula was found at initial abscess drainage, a second EUA need not be carried out where skin derived organisms were cultured. Furthermore, as almost 40% of patients had

undergone previous surgery, almost exclusively for sepsis at the same site, they declared that patients with acute anorectal sepsis had previously been poorly managed.

Results from these two units were at slight variance, however as only the latter study was prospective, a further combined prospective study was undertaken, where specimens of pus rather than swabs were obtained (Eykyn & Grace, 1986). In 53 of the 80 cases where microbiology and surgical findings were available, a fistula was found. Analysis showed that the isolation of colonic anaerobes, particularly *E. Coli* or *Bacteroides fragilis* was highly indicative of a fistula, and those yielding *Staph. Aureus* or non “gut-specific” anaerobes were highly unlikely to have a fistula, suggesting that only the former group should undergo a second EUA if a fistula were not demonstrated at initial presentation. This study also emphasised that a proportion of anorectal abscesses are not related to intersphincteric sepsis, and are probably derived from apocrine gland infection. However, Nicholls et al (1990) reported that *Bacteroides* (i.e. *fragilis*) subtyping was not available in most UK district hospitals, and therefore culture was meaningless. Lunniss and Phillips (1994) prospectively compared surgical and microbiological assessments for acute anorectal sepsis in 22 patients. Whilst their study confirmed earlier reports that the presence of gut organisms was 80% sensitive and specific for detecting an underlying fistula, they found surgical demonstration of intersphincteric sepsis using a radial incision both 100% sensitive and specific, and well within the capability of a surgical trainee. They concluded that microbiological findings were rarely necessary, however, the surgical trainee in question was a colorectal trainee with expertise in fistula-in-ano.

In chronic fistula-in-ano, whilst the type of organisms are similar to the acute setting, these have proved hard to culture from granulation tissue obtained at surgery, even using enriched culture mediums (Seow-Choen, et al, 1992). Furthermore, organisms have not been demonstrated histologically (Lunniss et al. 1993).

Persistence

Goodsall and Miles (1982) believed that fistulas persisted because of the constant action of the sphincter muscles and also movement caused by breathing, defecation and strenuous activity. While fistula are not maintained by virulent organisms (Seow-Cheon, et al., 1992), their persistence is not fully understood, and may relate to non-specific epithelialisation, possibly from epithelial in growth from either internal or external openings (Lunniss et al. 1995b)

Fistula in Other Species

McColl (1967), who studied 20 different species, reported that whilst many had anal glands, only those with human type intramuscular glands, such as dogs, pigs and cattle, developed fistula-in-ano. McColl attempted to create a fistula model, by ligating outlet ducts of canine anal scent glands, however this experiment failed. McColl concluded that he should have ligated ducts of anal intramuscular glands. Killingsworth et al (1988) noted fistula-in-ano in middle-aged male dogs, believing that hereditary factors were important in their pathogenesis.

Fistula Classification

Fistula classification, which has altered over time to reflect changes in the understanding of anorectal anatomy and fistula pathogenesis, helps determine the surgical strategy. Goodsall and Miles (1982) described the complete, blind external or blind internal fistula, with the latter subdivided into subcutaneous, submuscular and submucous.

Milligan and Morgan (1934) recognised the importance of the anorectal ring at the level of puborectalis (Figure 1, page 33). They felt that fistulas passing below the ring, classed as anal, could be laid open without compromising function, however anorectal fistulas passing above it could not. Eisenhammer (1958) clarified that the high submucous fistulous abscess was in fact situated within the intermuscular plane. Goligher *et al* (1976) took account of the relationship of the track to the levator ani. The ischiorectal fistula rose to the apex of the ischiorectal fossa, however the rare pelvi-rectal fistula (Figure 6, page 48.) had an upward extension penetrating levator ani. Thompson (1962) divided fistula into simple to treat, in 95% of cases, and complex and difficult to treat in 5%. Complex tracks included those with an internal opening above the anorectal ring, or those with a horseshoe around three quarters of the EAS circumference.

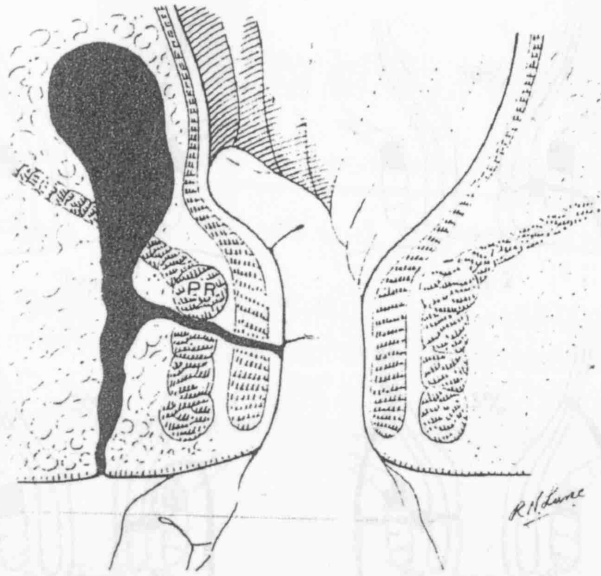


Figure 6: The Pelvirectal fistula.

Infection has spread through levator ani and induration is felt through the rectal wall.

(Parks AG, Gordon PH & Hardcastle JD 1976 A classification of fistula-in-ano. *Br.J.Surg.* 63: 1-12. ©British Journal of Surgery Society Ltd. Reproduced with permission; granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

Parks classification, in common use today (Parks, Gordon, & Hardcastle 1976), is modified from Steltzner's (1959) earlier description, and is based upon 400 patients with fistula-in-ano treated at St. Mark's Hospital. Central to this classification is the cryptoglandular hypothesis (Eisenhammer 1958), where most fistula result from infected intersphincteric anal glands, and the acute abscess drains along pathways of least resistance to create a primary track.

The primary track usually has one anal canal or rectal internal opening, and one external opening. Interphincteric fistulas (45%) track down between external and internal sphincters, though occasionally extend cranially and may open into the rectum.

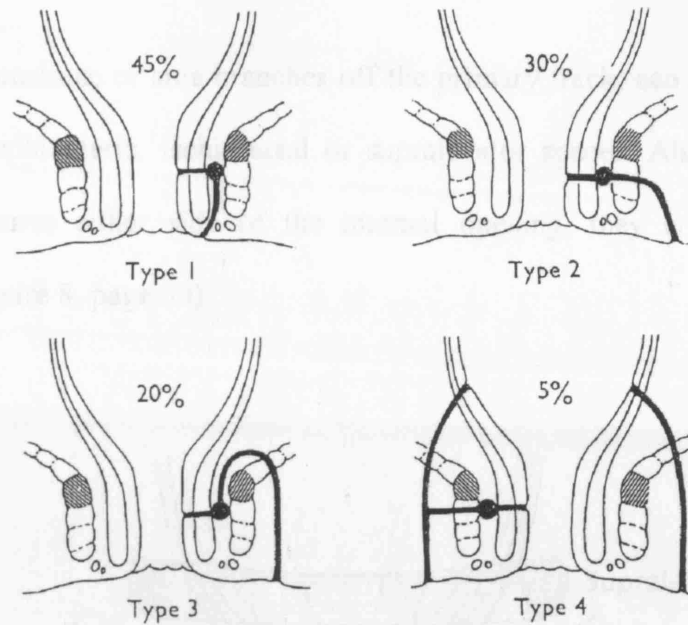


Figure 7: Parks classification: the four main anatomical types of fistula.

The external sphincter mass is regarded as the keystone and the terms “trans-“, “supra-“ and “extra-“ refer to it. Type 1: Intersphincteric; Type 2: Trans-sphincteric; Type 3: Suprasphincteric; Type 4: Extrasphincteric

(Parks AG, Gordon PH & Hardcastle JD 1976 A classification of fistula-in-ano. *Br.J.Surg.* 63: 1-12. ©British Journal of Surgery Society Ltd. Reproduced with permission; granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

Trans-sphincteric fistulas (30%) cross the EAS at varying levels to pass into the ischiorectal fossa. Suprasphincteric fistulas (20%) loop over puborectalis, descending through the levator and the ischiorectal fossa. Extrasphincteric fistulas (5%) have a rectal internal opening, descending caudally to the perineum, and are unrelated to the anal canal. These four main types and their incidences are displayed in figure 7,(page 49).

Parks did not describe superficial fistulas, however these tracks, which remain superficial to the sphincters, later accounted for 16% of 793 patients studied at St. Mark's (Marks & Ritchie 1977) and are common nomenclature today.

Secondary extensions, or side branches off the primary track, can extend in superficial perianal, intersphincteric, ischiorectal or supralelevator spaces. Also termed abscesses, when they course either side of the internal opening, they are termed horseshoe extensions (Figure 8, page 50).

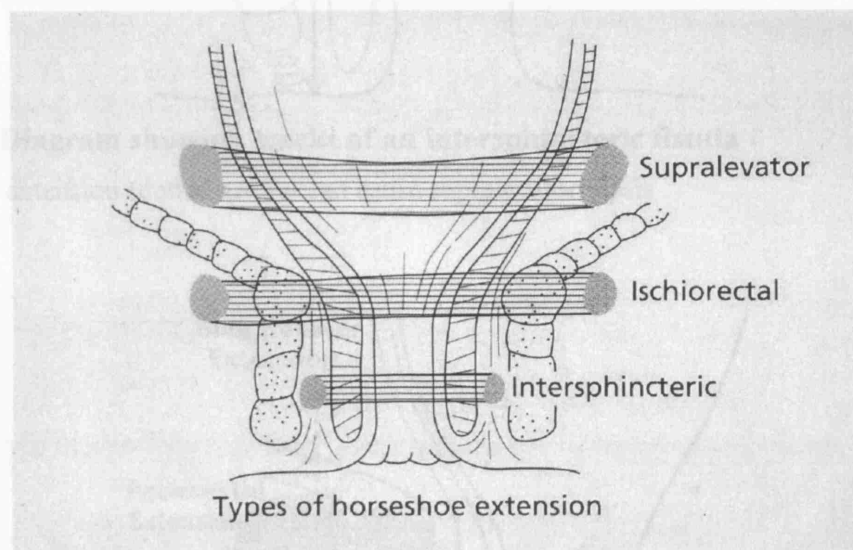


Figure 8: The three planes in which horseshoeing occurs

(adapted from - Parks AG, Gordon PH & Hardcastle JD 1976 A classification of fistula-in-ano. *Br.J.Surg.* **63**: 1-12. ©British Journal of Surgery Society Ltd. Reproduced with permission; granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

Parks emphasised that supralelevator sepsis could arise from pelvic disease, upward extension of an intersphincteric fistula (Figure 9, page 51), or upward extension of a trans-sphincteric fistula (Figure 10, page 51), and stressed the importance of correct diagnosis of fistula origin before drainage.

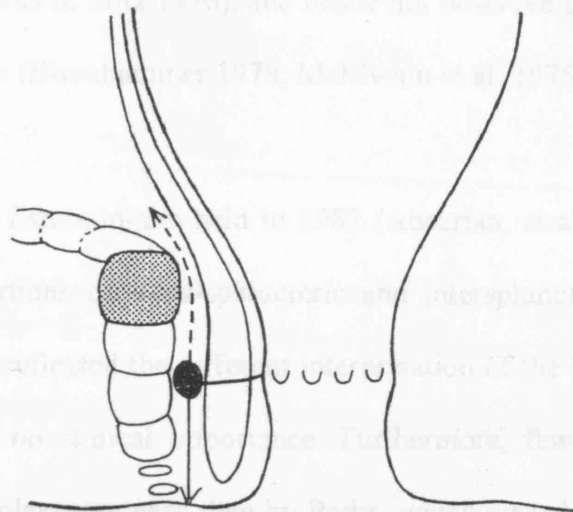


Figure 9: Diagram showing tracks of an intersphincteric fistula

Upward extension (dotted arrow) can cause supralelevator sepsis

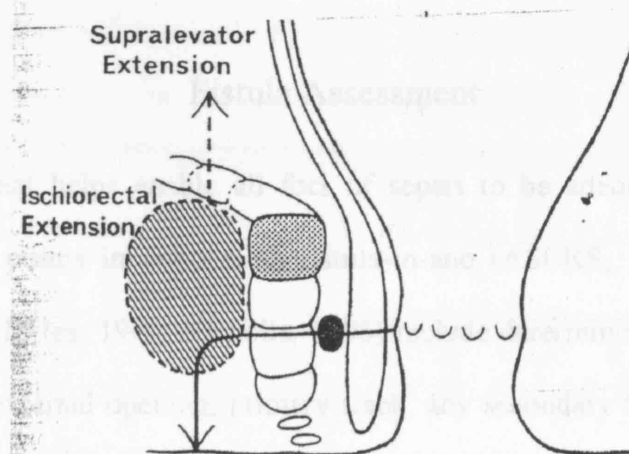


Figure 10: Trans-sphincteric fistula with avenues of extension

(Fig 9 and 10: Marks CG & Ritchie JK 1977 Anal fistulas at St Mark's Hospital. *Br.J.Surg.* 64: 84-91. ©British Journal of Surgery Society Ltd. Reproduced with permission; granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

Whilst Parks classification is widely applied, others suggest suprasphincteric fistulas to be iatrogenic. Fucini (1991), who studied 201 patients with perianal sepsis, only found supra- or extra-sphincteric tracks in patients with recurrent sepsis. Further, Eisenhammer (Eisenhammer 1978; McElwain et al. 1975) suggested that the complex fistulas observed in Parks' series were created by a general surgeon (Parks, Gordon, &

Hardcastle 1976; Parks & Stitz 1976), and hence not observed in the clean cases treated by him or McElwain (Eisenhammer 1978; McElwain et al. 1975).

In a symposium on fistula-in-ano held in 1987 (Abcarian, et al. 1987), it was felt that the different proportions of trans-sphincteric and intersphincteric fistulas from each study group merely reflected the different interpretation of the lower border of the IAS and EAS, and had no clinical importance. Furthermore, fewer suprasphincteric and extrasphincteric fistulas were seen than by Parks, which was also noted in a later study from St. Mark's Hospital (Malouf et al. 2002)

Fistula Assessment

Accurate assessment helps enable all foci of sepsis to be adequately treated during surgery. The key points in delineating fistula-in-ano (ASCRS, 1996a; Choen et al., 1991; Goodsall & Miles, 1900; Nicholls, 1996) include determining the location of the internal opening, external opening, primary track, any secondary track and presence of any underlying disease (Winslett, Allan, & Ambrose, 1988). Failure to correctly identify and treat any one of these components can lead to fistula recurrence (Garcia-Aguilar et al., 1996).

Clinical Assessment

Most patients present with acute anorectal sepsis or a chronic perianal discharge and may report previous surgery for similar symptoms. In each case, a full history, careful examination and proctosigmoidoscopy are required.

Technique of clinical examination

Usually the external opening is clearly visible, however it may be absent or hard to depict in the presence of scarring. Most fistulas obey Goodsall's rule (Goodsall & Miles, 1900). This states that an external opening situated behind the transverse anal line will open into the anal canal in the midline posteriorly, whereas an anteriorly placed external opening is usually associated with a radial track. Internal openings may be detected by palpation, where they feel like a pit or grain of rice, or visualized if a bead of pus is evident or also revealed by dimpling if traction is placed at the site of the external opening (Ross, 1988). They are usually sited at dentate line level, which can be appreciated by an increased slipperiness as one palpates the cranially sited anorectal mucosa.

Induration or asymmetry between the right and left anorectum on palpation suggests secondary extension, although Parks recognized difficulties differentiating supralelevator and infralevator sepsis (Parks, Gordon & Hardcastle, 1976). Supralelevator induration can feel like bone in front of the coccyx or sacrum (Seow & Philips, 1991), which can be inadvertently overlooked as normal. This induration can be caused by a supralelevator extension, suprasphincteric or extrasphincteric primary tracks, high intersphincteric extension or an extension into the roof of the ischioanal fossa (Figure 11, page 54). Marks and Ritchie found supralelevator extensions uncommon compared to the more frequently associated trans-sphincteric fistula and ischiorectal extension (Marks & Ritchie, 1977).

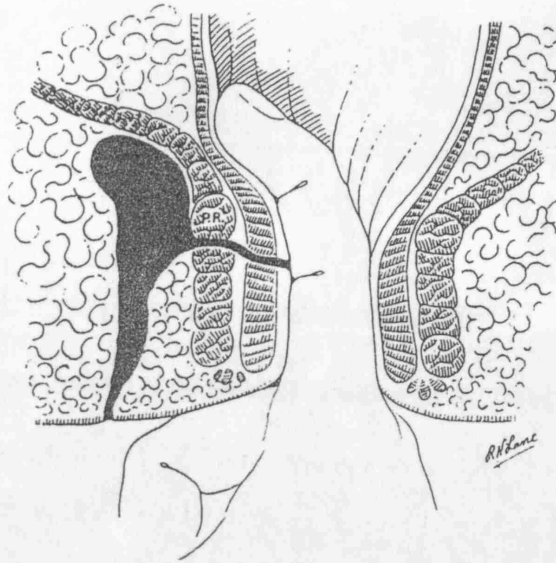


Figure 11: The classic St. Mark's anorectal fistula.

Induration is felt above the anorectal ring, but the inflammation is restricted to the ischioanal fossa.

(Parks AG, Gordon PH & Hardcastle JD 1976 A classification of fistula-in-ano. *Br.J.Surg.* 63: 1-12. ©British Journal of Surgery Society Ltd. Reproduced with permission; granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.)

When superficial, the primary track feels like a cord between the external opening and anus, however where it is high the track may be impalpable on the perineum. Asking awake patients to contract the anus, particularly where a seton is present, enables assessment of the amount of sphincter below the track.

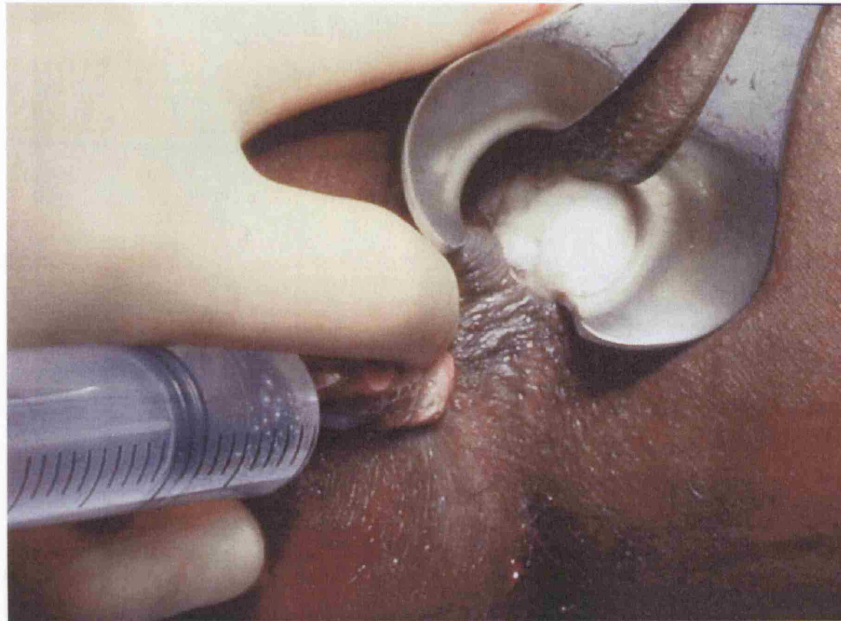


Figure 12: Hydrogen Peroxide helps locate the internal opening at EUA

If the track is very narrow, passage of a lacrimal probe (Figure 14, page 57) can help. At surgery, patients may be placed in lithotomy or jack-knife positions (Thomson & Parks, 1979). Hydrogen peroxide instilled from the external opening (Figure 12, page 55), can assist internal opening detection (Glen, 1993). Injecting methylene blue dye can also help, though may stain the tissues (Dunphy & Pikula, 1955). Many regard probing as part of the operative procedure, suggesting its avoidance in awake patients (Dunphy & Pikula, 1955; Nicholls, 1996). Gentle use of a Lockhart-Mummery probe (Figure 13, page 56) from internal or external openings often helps delineate the primary track (Hawley, 1975). However injudicious probing can create false tracks (Parks, Gordon & Hardcastle, 1976)



Figure 13: Lockhart-Mummery Probes

If the track is very narrow, passage of a lacrimal probe (Figure 14, page 57) can help demonstrate an “hour-glass” deformity (a narrowing in the fistula lumen).

During surgery, circumferential exploratory incisions are useful as they do not divide the sphincter, and can provide a better angle to facilitate probing of deep tracks. Self-retaining retractors may also be useful in this circumstance. Secondary tracks are implied by the presence of persistent granulation tissue that does not curette away at EUA (Grace, 1990)

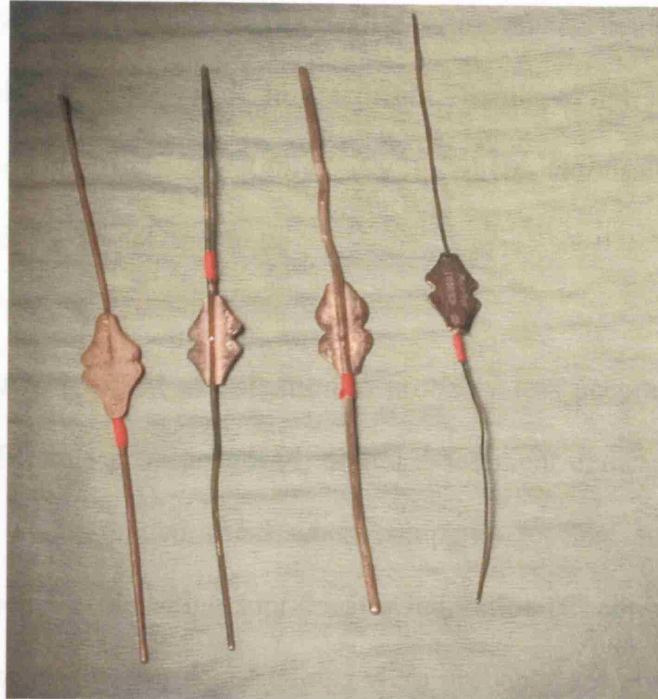


Figure 14: Lacrimal probes.

These probes are narrower and can help negotiate an hourglass deformity

Accuracy of clinical assessment

While some believe fistula-in-ano easily treated by surgery alone (Shouler et al, 1986), Sangwan et al (1994) found assessment of seemingly simple fistulas incorrect in approximately 30 out of 461 patients (6.5%), who recurred because of inadequate evaluation. In 16 of these the internal opening had been missed at initial surgery, a strong predictor of subsequent relapse (Lilius, 1968, Sainio & Husa, 1985b), while 6 had secondary tracks missed. However, 5 recurrences were due to skin bridging, a factor that can be diminished by use of the Salmon's back cut procedure (Thompson, 1962)

Gunawardhana and Deen (2001) compared Goodsall's rule to hydrogen peroxide instillation at EUA for internal opening detection. Whilst Goodsall's rule only had a positive predictive value of 59% in 35 patients, 34 (97%) internal openings were

detected using hydrogen peroxide. Goodsall's rule was particularly inaccurate for posterior external openings, and in recurrent fistula, contradicting an earlier retrospective review (Cirocco & Reilly, 1992), where Goodsall's rule was more accurate for posterior external openings.

Preoperative outpatient digital examination is probably less accurate than EUA, even without the use of fistula probes. Indeed, digital assessment under anaesthesia without probes was more accurate than AES when compared to final surgical findings. In particular it was better at detecting supralelevator induration (Cheon et al. 1991). Whilst the authors recognised that surgical findings were probably not always correct, others have continued to use these as a marker against which to compare their assessments.

Poen et al (1998) only correctly diagnosed primary tracks during preoperative digital examination, together with probing, in 38%. Internal opening and extension detection was 71% and 60% accurate, respectively. Ratto et al (2000) found digital examination with probing accurate in detecting 65% of primary tracks, 73% of secondary tracks, 81% of horseshoe extensions and 23% of internal openings. In both of these studies, hydrogen peroxide enhanced AES was more accurate.

Van Beers *et al* (1994) found preoperative MRI more accurate in 12 out of 13 cases than digital evaluation, accurate in only 8 cases. Beckingham *et al* (1996) prospectively studied patients undergoing preoperative digital evaluation and surgical assessment, and found that both techniques underestimated fistula complexity, also emphasising the importance of follow-up to determine the true reference standard as surgery was often

incorrect. In a further study, Chapple et al (2000) clearly showed that MRI was a better predictor of outcome, as it often depicted sepsis which surgery had failed to locate.

Schwartz *et al* (2001) found surgical EUA accurate in 90% of cases in patients with Crohn's disease, however 100% accuracy could be achieved if EUA findings were combined with findings obtained by either AES or MRI. Certainly, investigators have traditionally used surgical findings as their gold standard, however the work of Schwartz *et al* (2001) and other studies assessing outcome and therapeutic impact of fistula imaging suggest not only that accurate imaging might assist EUA, but also that future reference standards should incorporate findings at outcome (Beets-Tan et al, 2001; Garcia-Aguilar, et al, 1996; Lunniss et al., 1992,; Zbar et al., 1988)

Fistula Imaging

The relative merits of fistula imaging modalities are now discussed.

CT

Computed axial tomography is inaccurate for fistula classification because its intrinsic tissue contrast is so poor, although this technique may be helpful in the assessment of pelvic collections (Schratter-Sehn et al. 1993).

Fistulography

Fistulography is simple, though results have been disappointing. Contrast injection via the external opening may only show part of the track system, especially where extensions are distant or secretions block the lumen. Furthermore, as the sphincter complex and levator ani are not visualised on fluoroscopy (Figure 15, page 61), one cannot accurately classify tracks. Additionally, contrast can reflux into the rectum and lead to erroneous reporting of an extra-sphincteric fistula (Halligan, 1998). Henrichsen and Christiansen (1986) found fistulography unhelpful in patients after drainage of acute sepsis, as only 2 out of 10 fistulas were correctly diagnosed. Kuijpers and Schulpen (1985) only found fistulography accurate in 4 out of 25 cases (16%) assessed retrospectively, although Weisman et al (1991) found fistulography altered management and revealed unexpected findings in 48% of a selected group. In practice, fistulography has a limited role though is probably most useful where a fistula is suspected to result from intra-abdominal disease, or when the external opening lies distant from the anus.



Figure 15: Contrast fistulography.

It is not possible to determine the level of this collection, as levator cannot be seen.

Anal endosonography

Endosonography (Figure 16, page 62) is no more uncomfortable than digital examination (Bartram, 1992) taking only about 5 minutes to perform. AES was the first technique to directly visualise the sphincter in detail (Law & Bartram, 1989). Initial enthusiasm that AES would accurately classify fistula-in-ano, with high detection rates for primary tracks (92%) (Law et al 1989) was not supported by a second study (Choen et al., 1991) where AES was no more accurate than digital examination, probably due to field-of-view limitations secondary to loss of probe contact in the proximal canal. However, AES has since been shown to assist decision-making during fistula surgery (Deen et al., 1994) also providing additional information in complex cases (Lindsey et al., 2002).



Figure 16: 10MHz anal ultrasound probe.

This is no bigger than the index finger

The internal opening was initially inferred by continuity between the intersphincteric track and the internal sphincter (Figure 17, page 63) (Choen et al., 1991), however an apparent IAS defect caused by local inflammation, and a defined subepithelial track associated with a localised sphincter defect also predict its site (Cho 1999). The overall sensitivity of all these signs is 94%, specificity of 87% and positive predictive value of 81%. The site of the internal opening is noted longitudinally relative to the dentate line level, which is assumed to lie just below the mid-point of the IAS (Tsunoda et al., 1993).

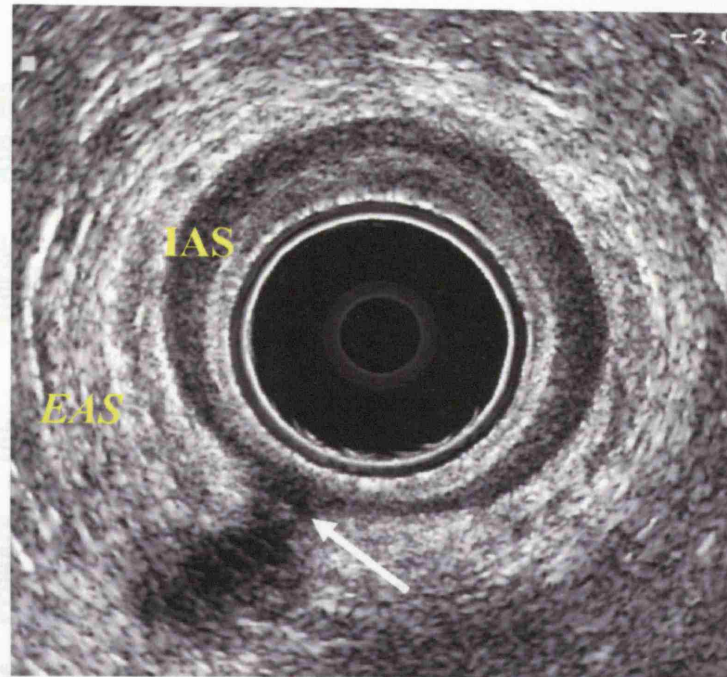


Figure 17: Fistula detected using AES:

Trans-sphincteric fistula, with internal opening (arrowed).

IAS=internal, EAS=external sphincter

The external opening is rarely visible using AES (Lunniss et al., 1994), as this usually lies below the anus, and so outside the field-of-view. Hydrogen peroxide, a strong ultrasound reflector, might enhance AES identification of fistulous tracks (Cheong et al. 1993; Kruskal, Kane, & Morrin 2001), although its true efficacy needs further determination (Poen, et al. 1998; Ratto, et al.. 2000; Sloots et al. 2001; Sudol-Szopinska, Jakubowski, & Szczepkowski, 2002). A list of current studies assessing fistula with AES is encompassed in Table 1 (page 64). The majority of these studies relate the accuracy of AES to surgical findings and do not include outcome to determine the “truth.”

Table 1: Endoanal ultrasound in the evaluation of anal fistula

Concordance with surgical findings in classifying the primary track, identifying internal openings, abscesses and horseshoe or secondary extensions. ns=not stated in article; * patients who have had hydrogen peroxide injected into their external fistulous opening during anal endosonography; + includes both primary and secondary tracks. ** comparison made to standard defined by arbitration

| Authors | n | Recurrent | Probe Mhz | Primary | Int. opening | Horse-shoe | Abscess |
|---|-----|-----------|-----------|---------|--------------|------------|---------|
| Law, Talbot, Bartram, & Northover (1989) | 22 | ns | 7 | 92% | 67% | 100% | 75% |
| Choen, Burnett, Bartram, & Nicholls (1991) | 36 | ns | 7 | 80% | 73% | ns | ns |
| Cheong, Noguerras, Wexner, & Jagelman (1993) | 2 | 100% | 7 | Ns | ns | 100%* | 100%* |
| Cataldo, Senagore, & Luchtefeld (1993) | 19 | ns | 7 | 63% | 28% | ns | Ns |
| Lunniss, Barker, Sultan, Armstrong, Reznick, Bartram, Cottam, & Phillips (1994) | 20 | 57% | 7 | 65% | 50% | 50% | 62% |
| Deen, Williams, Hutchinson, Keighley, & Kumar (1994) | 18 | 100% | 7 | 94% | 11% | 56% | Ns |
| Hussain et al. (1996) | 28 | 86% | 7 | 61% | 43% | 100% | 43% |
| Poen, Felt-Bersma, Eijssbouts, Cuesta, & Meuwissen (1998) | 21 | 38% | 7 | 62% | 5% | 50% | 67% |
| Orsoni et al. (1999) | 22 | 23% | 7 | 95%* | 48%* | 100%* | 100%* |
| Ratto, Gentile, Merico, Spinazzola, Mangini, Sofo, & Doglietto (2000) | 26 | 0% | 10 | 82%+ | 88% | Ns | Ns |
| Gustafsson et al. (2001) | 23 | 87% | 10 | 50% | 54% | 81% | 65% |
| Schwartz, Wiersema, Dudiak, Fletcher, Clain, Tremaine, Zinsmeister, Norton, Boardman, Devine, Wolff, Young-Fadok, Diehl, Pemberton, & Sandborn (2001)** | 38 | ns | 10 | 77%* | 54%* | 92.3%* | 89%* |
| Lindsey, Humphreys, George, & Mortensen (2002) | 143 | 10.5% | 10 | 61% | 74% | ns | 65% |
| Ortiz et al. (2002)* | 151 | ns | 10 | 91% | ns | ns | ns |
| Lengyel, Hurst, & Williams (2002)* | | | | | | | |

Magnetic Resonance Imaging

Basic Principles

Whilst the exact mechanism of MRI is beyond the scope of this thesis this is well documented elsewhere (Armstrong & Keevil, 1991). In summary, substances become magnetised to different extents following the application of a magnetic field. When the body is exposed to radiofrequency, proton realignment occurs. When this frequency is turned off, energy is emitted, the strength of which is proportional to the proton density. Density varies in different tissues, depending on their water content. MRI relies on the fact that different tissues recover at different rates following radiofrequency application, hence emitting different strength signals. This is constant for a particular tissue in a given magnetic field. “Spin-spin interaction”, caused by proton interaction and signal reduction, results in T2 decay. Gadolinium is a paramagnetic substance, and it stimulates T1 recovery due to this magnetic susceptibility. Gadolinium is often administered as an MR contrast medium, as tissues enhance to varying degrees following its injection. Short Tau Inversion Recovery (STIR) sequences are frequently used in fistula imaging. During STIR sequences, signals from fat, whose T1 recovery is fast, are suppressed, and inflammation in fistula tracks shows up as bright white (Figure 18, page 66).

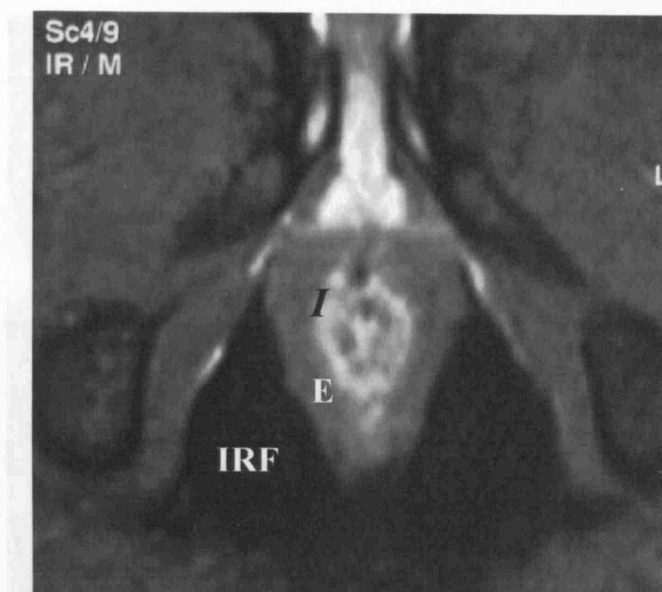


Figure 18: Axial STIR sequence MRI.

The ischiorectal fossa (IRF) is black as the fat is suppressed, and the internal (I) and external (E) sphincters are depicted.

Technique

STIR sequence MRI (Lunniss et al., 1992) involves no contrast, internal coils or ionising radiation and provides multiplanar imaging and soft tissue differentiation that help show the relationship of the track system to the anal sphincter complex. T2 weighted sagittal sequences (Figure 19, page 67) are employed to accurately localise the anal canal, with axial and coronal STIR sequences then performed perpendicular and parallel to its longitudinal axis. Using STIR imaging, the IAS is brighter than the EAS (Figure 18, page 66).

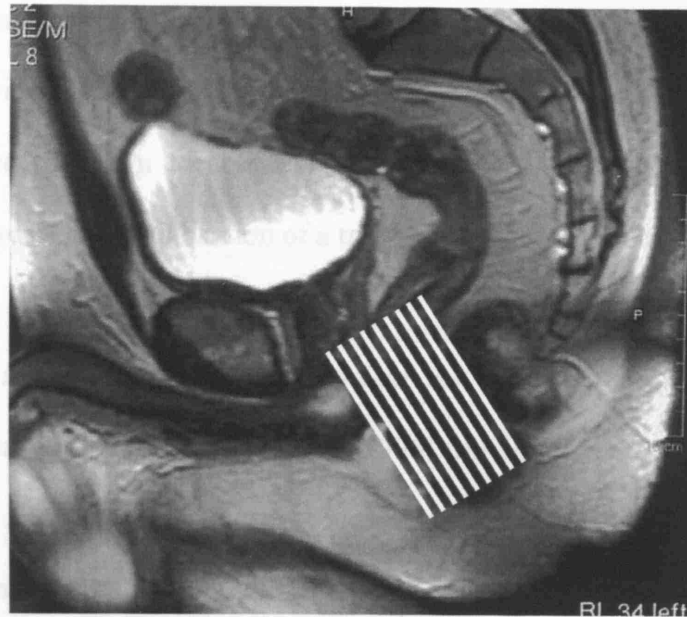


Figure 19: T2 weighted sagittal planning scan.

The anal canal axis is localised by the parallel lines.

Whilst STIR sequence MRI is simple, others advocate high-spatial-resolution MRI (Beets-Tan et al., 2001). T2-weighted fat suppression sequences (Halligan, Healy, & Bartram 1998) or T1-weighted dynamic contrast enhanced MRI (DCEMRI) using intravenous gadolinium (Spencer et al. 1996; Spencer, Ward, & Ambrose 1998). Alternative means of track contrast enhancement include either saline injection (Myhr et al., 1994) or rectal gadolinium (Sabir et al., 2000).

Whatever the technique used, it must be able to highlight both pus and granulation tissue against adjacent structures. Most importantly, some form of fat-suppression should be employed if using fast spin echo sequences since the high signal normally returned from fat can easily hide an active track or abscess. DCEMRI, using fast low angle shot software to create blocks of eleven 5-7mm thick contiguous slices in a 19sec acquisition time at 10, 30

and 50sec after gadolinium injection (Spencer et al., 1996), highlights inflamed tissue, but not fluid, bright via the capillary circulation, whilst STIR provides a high signal from both fluid and inflamed tissue. In combination, these techniques can help differentiate active inflammation, fibrosis, epithelialisation of a track, abscesses and mucous.

Although endocoils provide superior anatomical resolution of fistula disease within the sphincter (deSouza et al. 1998; Stoker et al. 1996), the improved spatial resolution using body-coil makes this technique more accurate in prospective comparison (Halligan & Bartram, 1998) and in combination with the pelvic phased array coil further sequences are rarely required.

Accuracy and efficacy of MRI for fistula-in-ano

The entire value of imaging anal fistula hinges on surgery not always being correct. There has been considerable interest in using MRI for preoperative fistula classification ever since a study of 16 patients with cryptoglandular fistulas found that STIR sequence MRI correctly predicted classification in 14 (Lunniss et al., 1992). Furthermore, whilst surgery was apparently normal in the remaining two, both later represented with sepsis at the site initially predicted by MRI (Lunniss et al., 1992) suggesting that MRI may actually be superior to EUA and could also identify features that predicted clinical outcome. A follow-up study of 35 patients showed that MRI was correct in 33 (94%) (Lunniss et al., 1994). Subsequently, Beckingham et al (1996) reported a sensitivity of 97% and specificity of 100% for MRI detection and classification of fistula in 42 subjects, four of whom were misdiagnosed during EUA, and that MRI better predicted fistula complexity than either

digital rectal examination or surgical exploration. An interesting series of studies from the same group separately classified patients on the basis of findings at preoperative MRI and subsequent EUA, and revealed that MRI was the better predictor of outcome (Chapple et al., 2000; Spencer et al., 1998).

Zbar et al (1998) found that MRI provided additional information in one of 10 patients with complex perianal sepsis. Scholefield et al (1997) assessed its role in seemingly simple fistulas, and reported that MRI precipitated additional surgery in only one of 27 patients, however, admitted that their radiologist was unfamiliar with the technique which might have prejudiced their results. Beets-Tan *et al.* (2001), using an experienced radiologist, found that MRI provided important additional information in 21% of patients undergoing EUA. MRI was 100% sensitive for detecting the primary track, 96% for abscesses, 100% for horseshoe extensions and 96% for internal openings. Benefit was altogether greatest in those with Crohn's (40%), versus recurrent (24%) and primary fistulas (8%).

MRI versus AES

Comparison between MRI and AES is difficult, as surgery has been considered the gold standard in most studies, which is incorrect. While two series, both with Crohn's patients, have suggested that AES is more accurate than MRI, Orsoni *et al* (1999) only used the body coil, and did not have the benefits of increased spatial resolution obtainable using the pelvic phased-array coil. Furthermore, Schwartz et al (2001) reported that any combination of two modalities from AES, MRI and EUA were 100% accurate. Maier et al (2001) found AES accurate in only 60% of cases, versus MRI in 84%. Hussain et al (1996) reported a

similar accuracy for intersphincteric tracks or fluid collections, but superior MRI detection of trans-sphincteric tracks and internal openings. Lunniss et al (1994) reported a poorer specificity of AES for supralelevator or ischiorectal extension detection in a study of 20 patients. Gustafsson et al (2001) found AES complemented by probing equivalent to body coil MRI. Whilst AES is a simple cheap examination and is useful in patients presenting with anal pain, accuracy is operator dependant, whereas abnormality is more definite on MRI and more easily appreciated by a clinician. The relative accuracies of these investigations deserves reappraisal following improvements in probe technology and understanding, and the realisation that comparisons need to include outcome data.

Treatment

Acute sepsis - relationship to fistula

Whilst acute perianal sepsis necessitates drainage, the cryptoglandular hypothesis additionally suggests that definitive treatment at this stage might prevent fistula formation. Eisenhammer (1985) advocated fistulotomy during abscess drainage, however Lockhart-Mummery (1975a) believed that injudicious probing in oedematous tissues could lead to iatrogenic tracks and that a staged approach was safer. The same is advocated in childhood, where although the majority of fistula are simple and fistulotomy may be undertaken at acute presentation (Piazza & Radhakrishnan, 1990) others suggest this should be delayed for a second EUA (MacDonald, Wilson-Storey, & Munro, 2003). These different viewpoints have led to much interest in not only who performs acute surgery, but also what type of operation is performed.

The incidence of fistula-in-ano in patients presenting with perianal sepsis is extensively documented. Chrabot et al (1983) found that 44 (45%) of 97 patients presenting with recurrent anorectal abscesses had a fistula. Scoma et al (1974) retrospectively studied 266 patients who had abscesses drained under local anaesthetic. No probing or fistulotomy was attempted at initial surgery. On follow-up, 66% developed a fistula. Read and Abcarian (1979) prospectively reported on a young, mostly black, population of 474 patients with anorectal abscesses. Of these 34% had fistula, of which 97% were laid open at the initial operation with few readmissions or complications. Chrabot et al (1983) felt that experienced surgeons should undertake initial surgery, and hence perform fistulotomy if

appropriate, thus avoiding many further unnecessary operations. Winslett et al (1988) reached a similar conclusion, particularly as 12% of patients presenting with acute anal sepsis also had occult disease.

Buchan and Grace (1973), who had retrospectively assessed 183 patients with acute sepsis, reported that wound “saucerisation” increased inpatient stay, instead suggesting incision, exploration and curettage. However this study did not comment on differences in abscess size between the groups. In a retrospective study, Vasilevsky and Gordon (1984) reported on 103 patients who underwent only incision and drainage of perianal sepsis and were followed-up ranging from one to 106 months. None with an intersphincteric abscess developed a fistula, however of the 83 with perianal or ischiorectal abscesses, 11% developed recurrent abscesses and 37% fistula-in-ano. Vasilevsky and Gordon advised a policy of secondary fistulotomy in this group, as 52% needed nothing further done after simple local anaesthetic abscess drainage as an outpatient.

Henrichsen and Christiansen (1986) prospectively assessed 50 patients presenting with acute anorectal sepsis. On follow-up, they found that 26% developed a fistula after incision and drainage. Many of these were unaware of its presence.

Hamalainen and Sainio(1998) followed 170 patients for a median of 99 months after abscess drainage; whilst 37% developed a fistula, and 10% another abscess, they agreed with Vasilevsky and Gordon that unnecessary fistulotomy might be avoided in approximately 50%. Abscesses growing *E Coli* were more likely to develop a fistula than those growing other bacteria.

Kronborg and Olsen (1984) reported a randomised controlled trial comparing incision and drainage of perianal sepsis, versus incision and drainage plus the addition of curettage and suture under antibiotic cover; patients who additionally underwent suture healed quicker in the short-term, and although more likely to develop recurrent sepsis in the long-term, the overall healing time was quicker in this group. In those patients treated by abscess drainage and primary suture, Mortensen *et al.* (1995) subsequently found no benefit by the addition of gentamicin soaked implant.

Hebjorn et al (1987) performed a randomised control trial assessing the value of fistulotomy in acute perianal sepsis. They reported that patients undergoing incision and fistulotomy had significantly higher rates of flatus incontinence than those in whom simple drainage was performed. As recurrence rates were similar, they felt that they could not recommend routine fistulotomy. Schouten and van Vroonhoven (1991) performed a similar study with similar conclusions in 70 patients with both perianal and ischiorectal abscesses. Whilst 41% of the 34 who had simple incision and drainage later recurred, versus 2.9 % of the 36 who also had fistulectomy, incontinence was more prevalent in the latter group. They believed that as 60% would not need further surgery they could not justify routine acute fistulectomy based on their data. Again, Seow Choen et al (1993) could not recommend a selective policy of immediate fistulotomy. Tang et al (1996), performed a randomised controlled trial on patients with proven internal openings, and found a trend towards recurrence in those treated with incision alone versus fistulotomy. This study included those with trans-sphincteric and intersphincteric fistulas. Grace (1997) felt this latter study had been too small (45 patients in total), with inadequate follow-up.

Ho et al (1997) went on to perform a randomised controlled trial that specifically looked at patients with perianal abscess and hence intersphincteric fistulas, as the risk of incontinence in this group is small. Interestingly, they found no difference in degree of incontinence between those with perianal abscess undergoing simple incision and drainage and those who underwent fistulotomy, whilst recurrence rates were higher after incision alone and concluded that if surgery was to be performed by experienced enough surgeons, fistulotomy could be undertaken at the outset.

Oliver et al (2003) performed a randomised control trial where 200 consecutive patients presenting with acute perianal sepsis underwent either simple drainage or drainage plus fistula treatment where appropriate. If fistulas were low and simple they were laid open, though if high or complex they were treated with progressive seton management. Those in the low group had low recurrence and low incontinence rates when treated by primary fistulotomy, however those with high tracks had higher degrees of incontinence when primarily treated using a staged-seton. The authors concluded that primary fistulotomy might be undertaken when fistulas are low, but delayed treatment was advocated where these are high.

Chronic fistula-in-ano

Lay open or fistulotomy

Lay-open of fistula-in-ano along its entire length by cutting down onto a fistula probe, allows a “gutter” or open wound to heal by secondary intention. Secondary extensions can

be similarly treated (Abcarian 1996; Parks, 1961; Parks, 1963; Thomson & Parks, 1979). McElwain et al (1966) instead advocated fistulectomy to excise a fistula or abscess. Kronborg (1985) compared fistulectomy with lay-open in a randomised trial of 47 patients, and found no difference in terms of recurrence and re-operation rates, although fistulectomy delayed healing. Healing is also delayed in subgroups of patients with HIV after fistulotomy, and surgery should probably only be undertaken in urgent cases (Nadal et al., 1998).

A randomised controlled trial performed by Ho et al (1998) reported faster healing after fistulotomy where marsupialisation is additionally performed. Whilst Gupta (2003) recently described faster healing with less bleeding comparing traditional cutting with radiofrequency fistulotomy, the data does not explain types of fistula studied.

Outcome of Treatment

Continuing problems after fistula surgery led to Lockhart Mummery's (1929) observation that a surgeon's reputation could be severely damaged by unsuccessful treatment. Surgery aims to achieve a balance between sepsis eradication and maintaining continence. However, other factors need consideration including the degree of pain, healing time, anal deformity and scarring, the need for a seton or stoma and overall satisfaction & quality of life.

Anal deformity

Some believe anal deformity predictive of incontinence (Christensen, Nilas, & Christiansen, 1986). Mazier (1985), in a retrospective study, certainly confirmed the presence of keyhole deformities, though found that this did not always precipitate incontinence, and postulated that they might be avoided by fistulotomy rather than fistulectomy.

Quality of life

Sailer et al (1998) applied the Gastro-intestinal quality of life index to fistula-in-ano, and found that patients with fistula (n=22) or abscess (n=7) had similar scores to age matched controls. The conclusion, from this small study, that perianal sepsis does not affect quality of life seems contrary to clinical experience.

Satisfaction

Garcia-Aguilar et al (2000) hypothesised that many patients tolerated minor degrees of incontinence at the expense of fistula healing, however any effect on patient satisfaction was unclear. Of 300 patients who were mailed a questionnaire where greater than 1-year follow-up had been achieved, 139 described incontinence to some degree (46%). However, recurrence was described in 23 (8%), and overall 264 (88%) patients were satisfied with their treatment. Of those patients dissatisfied, fistula recurrence, incontinence and its effects on lifestyle and social functioning contributed significantly. They concluded that

continence preserving surgical procedures that didn't unduly increase recurrence might prevent a large proportion of patient dissatisfaction.

Continence

Faecal continence depends upon a fine interplay between sensory mechanisms of the anorectum, spinal and central nervous system, anal sphincter function and mechanical factors including rectal compliance, stool volume and stool consistency. Its exact mechanism is beyond the scope of this thesis. Suffice it to say, that continence may be affected to a variable degree after anal fistula surgery, and techniques such as anorectal physiology (Jorge & Wexner, 1993) help to provide quantitative measures of anorectal function, whilst continence scores have evolved enabling patients to relay their degree of continence to investigators (Parks 1975; Rockwood et al. 1999; Vaizey et al. 1999).

Whilst maintenance of puborectalis and the anorectal ring was thought by some as the only requirement to maintain continence after fistulotomy, high EAS division which may occur with high trans-sphincteric fistulas may indeed lead to impaired continence (Belliveau, Thomson, & Parks 1983). Indeed, Bennett (1962) reflected that it was “poor consolation for the fastidious patient who, after seventeen weeks off work for treatment of his horseshoe fistula, finds that his underclothes are stained brown instead of yellow!”

Belliveau et al (1983) studied 47 patients who underwent fistulotomy, with manometry. They found that EAS division in trans-sphincteric fistulas led to a lower anal pressure in the distal 3cm of the anal canal, and this was often associated with continence disturbance, and

while IAS division alone in trans-sphincteric fistulas did result in a lower distal anal canal resting pressure, there were few cases of incontinence.

Sainio and Husa (1985) retrospectively studied 199 patients using anal manometry approximately 9 years after fistulotomy. They found 34% of their population suffered minor incontinence problems. Moreover, those with high intermuscular fistula (intersphincteric) were more prone to incontinence. They found resting and contractile pressures lower in those with defective control. Interestingly, maximal contractile pressure was irrespective of the amount of sphincter divided. In an earlier prospective study, Sainio and Husa (1985a) had found distal anal canal resting pressure significantly reduced following fistulotomy, with significantly lower pressures in females versus males. They noted that defective control was associated with reduced squeeze pressure, and suggested that EAS division should be avoided particularly in females or if preoperative pressure was low.

Pescatori et al (1989) prospectively applied anal manometry to patients undergoing fistula surgery to determine whether it might help improve functional outcome. They compared the results of these 96 patients with another 36 who did not have manometry. Postoperative soiling was associated with a significant decrease in resting tone and voluntary contraction. Furthermore, a significantly lower rate of soiling was noticed in the manometry group, which was attributed to patients with low preoperative pressures undergoing seton placement rather than fistulotomy.

However, in a further prospective study performed by Lunniss et al (1994) 19 of 37 patients undergoing fistulotomy developed some defect in continence postoperatively. The severity of continence, anal canal squeeze pressure and anal canal length were similar when comparing those patients in whom the EAS was either preserved or divided, however those patients with incontinence had significantly lower resting pressure and higher sensory threshold than those who remained continent, suggesting that incontinence related primarily to IAS division and blunted mucosal sensation.

Van Tets and Kuijpers (1994) analysed continence disorders after fistulotomy. Using a questionnaire, they ascertained that minor degree of incontinence was present in 27% of patients (i.e. flatus intolerance, poor control of diarrhoea and soiling). Those factors predictive of incontinence included a high internal opening, increased amount of muscle divided in trans-sphincteric, extra-sphincteric and suprasphincteric versus intersphincteric fistulas. Incidentally, these complex fistulas were usually associated with extensions. Interestingly, they found that the seton-fistulotomy technique did not protect against the development of continence impairment, and suggested that incontinence probably related to several other factors, namely excessive traction by operative instruments, and damage of fine nerves when dividing extensions.

It is noteworthy that since Lunniss et al (1994) reported their findings, the ability to defer defecation has gained greater weight in modern scoring systems (Vaizey, et al., 1999), which may explain surgeons' continuing reticence to divide the EAS during fistula surgery.

A larger prospective study looked in detail at 45 adults who underwent fistulotomy of intersphincteric fistulas. Of these, poor continence control was observed in 38%. Unsurprisingly, there was a significant overall decrease in distal resting anal canal pressure. Incontinence was associated with female sex, and those who had a lower preoperative resting pressure. Incidentally, this group also tended to have lower maximal contractile pressures, suggesting that their EAS (although not divided), could not compensate for a disrupted IAS, hence leading to incontinence (Chang & Lin, 2003)

Recently, Cavanaugh et al (2002) assessed patients post fistulotomy with the faecal incontinence severity index questionnaire (Rockwood et al, 1999). In the 96 patients who responded, 41% had undergone lay-open of intersphincteric and 59% trans-sphincteric fistulas. Incontinence related to the amount of EAS cut at surgery, furthermore the quality of life of these patients related to the degree of incontinence they suffered. Fortunately, for those patients who become incontinent after fistulotomy, EAS repair achieves a satisfactory outcome for the majority (Engel et al. 1997)

It seems there is a role for attempting sphincter conservation in patients with fistula-in-ano, particularly if they fall into a high-risk group where fistulotomy attempted. Sphincter conserving therapies are discussed and investigated further in Chapters 9-11.

Recurrence

Whilst many fistula-in-ano are simple and easily cured by surgery (Shouler et al. 1986), recurrence is reported in up to 25% of cases following fistula surgery (Lilius, 1968). Fistula

may recur for several reasons; a failure of the technique such as fibrin sealant or advancement flap, further sepsis due to inadequate aftercare, perhaps caused by skin bridging, or failure to detect and eradicate all tracks or openings at initial surgery. In addition, recurrence rates generally tend to increase the longer the period of follow-up (Grace, 1997)

Sainio and Husa (1985b) reported on 199 patients 9 years after treatment. Whilst the overall recurrence rate following fistulotomy was 11%, recurrence rates were significantly higher for high anal fistulas at 26% when compared with the rest of the group. The main reasons for recurrence were missed tracks and openings, and failure to adequately lay-open the track.

Seow-Choen and Phillips (1991) reported on 24 patients with problematical anal fistulae at St. Mark's Hospital and determined reasons for failure. Recurrence occurred in 5 of these 24 patients due to a missed primary or secondary track, though in the majority was due to the need for staged procedures using a seton or a stoma. A good outcome was eventually obtained in the majority.

Recurrence was assessed by Garcia Aguilar et al (1996), who studied questionnaires returned from 375 patients who had undergone fistula surgery a median of 29 months previously. Three hundred and fifty one patients (97%) underwent fistulotomy, TSSF or cutting-seton treatment. Overall, 31 patients (8%) recurred. Recurrence was associated with complex fistulas, horseshoe fistula and previous fistula surgery. Furthermore, failure to identify the internal opening and the individual surgeon performing the procedure were also

prognostic. Barwood *et al* (1997) prospectively assessed 107 patients with fistula-in-ano. They noted an increased history of previous fistula or abscess surgery where patients had more complex disease. Furthermore, of the 7 patients who recurred during their study period, 6 had complex disease and recurrence was usually due to missed openings and tracks at the initial procedure. Table 2 (page 83) summarises recurrence following fistulotomy. It seems that recurrence due to missed tracks and openings remains a problem during fistula surgery, therefore strategies to guide EUA seem worthwhile.

Table 2: Recurrence rates after fistulotomy

| Author (Year) | No. | Recurrence (%) | Altered continence (%) |
|---|------|----------------|------------------------|
| Bennett (1962) | 108 | 2 | 36 |
| Hill (1967) | 626 | 1 | 4 |
| Lilius (1968) | 150 | 5.5 | 13.5 |
| Lilius (1968) (World) | - | 0.7-26 | 5-40 |
| McElwain, MacLean, Alexander, Hoexter, & Guthrie (1975) | 1000 | 3.6 | 7 |
| Parks & Stitz (1976) | 158 | 9 | 17-39 |
| Hanley et al (1976) | 41 | 0 | 0 |
| Ramanujam et al. (1984) | 1023 | 1.8-3.7 | Not stated |
| Khubchandani (1984) | 68 | 5.8 | Not stated |
| Vasilevsky & Gordon (1984) | 260 | 6.3 | 6 |
| Sainio & Husa (1985b) | 199 | 11 | 34 |
| Shouler, Grimley, Keighley, & Alexander-Williams (1986) | 115 | 8 | 12 |
| Sangwan, Rosen, Riether, Stasik, Sheets, & Khubchandani (1994) | 461 | 6.5 | Not stated |
| Barwood, Clarke, Levitt, & Levitt (1997) | 107 | 7 | Not stated |
| Malouf, Buchanan, Carapeti, Rao, Guy, Westcott, Thomson, & Cohen (2002) | 98 | 4 | 10 |

Chapter 3:

The Effect of Magnetic Resonance Imaging on Clinical Outcome in
Recurrent Fistula-in-ano: A Prospective Trial

Introduction

Whilst surgery cures most fistulas, recurrence occurs in up to 25% of cases (Lilius, 1968), especially when the fistula is complex. Complex fistulas are associated with secondary extensions (abscesses or tracks) from the primary track. Such extensions can commonly cause relapse because they frequently go unrecognised and thus remain untreated at the time of surgical assessment (Seow & Phillips, 1991). This emphasises the need for accurate pre-operative assessment in recurrent disease but this is notoriously difficult if the fistula is complex and there has been previous surgery (Garcia-Aguilar, et al., 1996). Attempts to accurately classify fistulas pre-operatively using AES (Cheon et al., 1991) have been disappointing, so that EUA remains the method of choice.

However, there is a growing body of evidence that MRI is more accurate than surgical exploration for fistula assessment and, most importantly, can demonstrate features likely to cause recurrence (Chapple, et al., 2000; Lunniss, et al., 1992; Schwartz, et al, 2001). Whilst pre-operative MRI may help direct surgical therapy in complex fistula (Beets-Tan, et al 2001) this does not seem to apply to simple fistula (Schofield et al., 1997). Despite this, assessment of outcome following MRI has been limited to series of relatively simple fistulas (Schofield et al., 1997). In contrast, it seems reasonable to expect the benefits of MRI to be maximal in patients with complex fistulas, especially those with recurrent disease, because these have the greatest likelihood of occult sepsis. This prospective study aimed to determine the therapeutic impact of MRI in patients presenting with recurrent

fistula-in-ano by investigating its effect on surgical approach and its consequences on clinical outcome.

Methods

Patients

All patients with recurrent fistula-in-ano were prospectively recruited and were identified in advance from outpatient booking forms. A pre- and post- intervention observational study design was used. To avoid selection bias, all consecutive patients presenting to participating surgeons with suspected recurrent disease were potentially eligible, irrespective of whether an MRI was felt clinically necessary or not. Disease was confirmed as recurrent by taking a history of previous fistula surgery from the patient at the subsequent outpatient visit. Referral origin, secondary or tertiary, was also noted.

Procedures

MR Imaging

A validated body- or surface-coil MRI protocol was used (Halligan, 1998; Lunniss et al., 1994). Usual contraindications to MRI applied (implanted metal devices, severe claustrophobia, weight greater than 150Kg). MRI was performed prior to scheduled EUA using a 1.0-T super conducting static magnet (Gyroscan T10-NT, Philips Medical Systems, London, UK). Patients were scanned supine under the direct supervision of an experienced

consultant gastrointestinal radiologist (SH, CIB) who was unaware of the clinical findings. Both radiologists had 3 years experience of MRI for fistula-in-ano at the commencement of the study, and had each reported approximately 300 studies at that time.

The long-axis of the anal canal was identified using a midline sagittal-localising scan and then axial and coronal STIR sequences planned with respect to the anal canal axis using the following scan parameters: TR/TE, 1500/15; field-of-view 375 mm; 256 x 256 matrix; 4mm slice thickness; 1mm interslice gap; 4 excitations. Sagittal T2-weighted images were employed in approximately 20% of cases at the discretion of the supervising radiologist when a pre-sacral extension was suspected from the axial and/or coronal STIR images, using the following parameters: TR/TE, 4563/150; field-of-view 350 mm; 256 x 256 matrix; 6mm slice thickness; 0.6mm interslice gap; 4 excitations. No intravenous contrast or endorectal/endoanal receiver coil was used.

Established criteria for MR diagnosis of a fistula were used, namely a high-signal track related to the sphincter complex (Halligan, 1998) using STIR sequences. The site of the internal opening was inferred from the presence of sepsis in the intersphincteric space (Halligan, 1998).

SURGICAL FISTULA SHEET

Patient name: _____

Date of operation:

Primary track

Sinus ☐

Superficial ☐

Intersphincteric ☐

Transsphincteric ☐

Suprasphincteric ☐

Extrasphincteric ☐

Internal opening

Site ____ o'clock

Level: Below dentate ☐

At dentate ☐

Above dentate ☐

Rectal ☐

Horse-shoeing

Intersphincteric ☐

Ischiorectal ☐

Supralelevator ☐

Abscesses

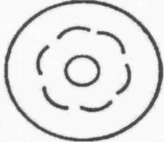
Superficial ☐

Intersphincteric ☐


Ischiorectal ☐

Supralelevator ☐


Anterior



Right



Left



Anterior

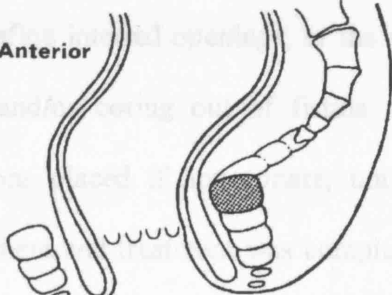


Figure 20: St Mark's Fistula Sheet

(Designed by Mr. JPS Thomson)

Scan findings were recorded by the supervising radiologist using a surgical fistula classification sheet (Figure 20, page 33) derived from Parks (Parks, Gordon & Hardcastle, 1976) and established in previous studies of MRI for fistula-in-ano (Beets-Tan, et al. 2001). This sheet detailed the course of the primary track and any associated extensions (tracks

and/or abscesses). If multiple fistulas were present, these were recorded together on the same sheet. The report was then sealed in an envelope together with laser images from the MRI examination so that they could be taken to the operating theatre at the time of subsequent EUA.

Examination under anaesthetic

All patients were examined under general anaesthetic in the lithotomy position. Consultant coloproctologists or year six senior specialist registrars, all of whom were experienced in fistula surgery, performed EUA. Clinical examination was performed as per usual practice (ASCRS 1996a), aided by Lockhart-Mummery and lacrimal fistula probes and/or instillation of hydrogen peroxide to help define internal openings, at the discretion of the operating surgeon. Surgical laying open and/or coring out of fistula tracks was then performed as deemed necessary, and setons placed if appropriate, until the operating surgeon was satisfied that his or her assessment and treatment was complete. At this stage the operating surgeon completed a fistula classification sheet identical to that used for the MRI report, detailing their findings regarding the primary track and any associated extensions: this was the 'initial' EUA assessment. The surgeon was also asked if they thought the subsequent MRI findings were likely to be of any value, indicating: - 'yes' or 'no' and also their confidence in their operative assessment using a visual analogue scale.

The MR images were then placed on a film-viewing box and reviewed by the operating surgeon in theatre, with the benefit of the fistula assessment sheet previously completed by the radiologist. If the MRI report and the 'initial' EUA assessment agreed, then surgery and

treatment was considered complete. However, if the surgeon felt additional surgical exploration and treatment was necessary in the light of information provided by MRI, this was then undertaken. However, the decision to undertake any additional surgery was left entirely at the discretion of the operating surgeon. Any additional surgery provoked by MRI was then documented, and if so, its nature and extent was recorded so that the therapeutic impact of MRI could be determined subsequently. At the end of any additional surgery, the surgeon completed a final fistula classification sheet for these patients, the 'review' EUA assessment, and indicated if they had found the MRI useful, stating 'yes' or 'no'.

Patient Follow up

Postoperative care was standard and patients were followed up in surgical outpatients as per usual practice. Special attention was paid to clinical evidence of fistula healing and clinical signs of recurrence following healing. Because fistula treatment was by permanent loose-seton in some cases, recurrence was defined as the need for further unplanned surgery. Recurrence was documented and subsequent management was performed according to usual clinical practice. Findings at any subsequent operations were also noted.

Statistical analysis

After surgery patients were divided into three groups based on the agreement between MRI and EUA findings: Group A, those patients in whom MRI and 'initial' EUA agreed; Group B, those patients in whom there was initial disagreement but where MRI and 'review' EUA agreed following additional surgical exploration contingent on the MRI findings; Group C,

those in whom disagreement remained. The primary track classification, location of the internal opening and the presence and location of any extensions were compared. Whether surgeons always, occasionally, or never acted on discrepant MRI findings was determined. Clinical outcome in the three groups was analysed at a median of 12 months following surgery (range 3-38 months). Categorical frequencies were analysed using Fishers exact test and chi-squared test for trend. Continuous variables (visual analogue scale) were analysed using the Mann-Whitney U test statistic. Differences in confidence across surgeons was analysed using ANOVA. Analysis was performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, Cambridge, UK). Statistical significance was assigned to a probability level of <0.05 .

Results

72 patients without MRI exclusion criteria were enrolled. One woman with severe claustrophobia could not tolerate scanning, leaving 71 for analysis. There were 53 men and 18 women, median age 42 years (range 17 to 65 years). The median number of previous operations for fistula-in-ano was 4, range 1 to 25. Fifty-four (76%) patients were tertiary referrals. Eleven had Crohn's disease. Forty (56%) were initially assessed in clinic by a Consultant coloproctologist. MRI scans were performed a median of 2 days prior to surgery, range same day to 183 days. Sixty of the 71 subjects (84.5%) had EUA within one month of their MRI. Longer delays were due to operation cancellation due to bed unavailability. All MRI was technically adequate and no patient was recalled for further imaging. EUA was performed by one of eight Consultant coloproctologists in 68 patients. Three different year six trainees operated on the remaining three. Median follow-up was 12 months, range 3 to 38 months, with no significant difference between groups ($p = 0.6$)

Agreement, therapeutic impact and outcome

Group A: Initial agreement between MRI and EUA.

'Initial' EUA agreed exactly with the disclosed MRI findings in 25 (35.2%) patients and no further surgery was deemed necessary in these. 22 (88%) had sepsis, 21 of which were fistulas (Table 3, Figure 20). No subject had more than one fistula and there were 12 (48%) patients with extensions (10 abscesses, 2 horseshoes). Three patients had Crohn's disease. On follow-up, three (12%) patients in this group needed further unplanned surgery due to

skin bridging following fistulotomy in two, and extended surgical drainage of a previously identified ischiorectal extension in a third.

Group B: Agreement between MRI and 'review' EUA.

'Initial' EUA conflicted with MRI findings in 15 (21.1%) patients but ultimate agreement was achieved in this group as a result of further surgical exploration contingent on the MRI findings (Figure 21, page 95). Thus the therapeutic impact of MRI was 21.1%. There were 18 fistulas (Table 3, page 94) in this group. MRI provoked further surgery that identified five unsuspected primary tracks (two extrasphincteric), and additionally correctly classified an intersphincteric fistula initially thought to be trans-sphincteric by the operating surgeon. There were 17 abscesses and 7 horseshoes in 12 patients. MRI identified 16 of these in 10 patients, additionally altering classification of extensions found at 'initial' EUA in two and preventing unnecessary exploration in one where an intersphincteric extension had been suspected by the surgeon but which was absent on MR imaging.

Table 3: Comparison of MRI and EUA findings

| | Patients in whom EUA and MRI | | | | |
|-------------------------------------|------------------------------|---------------------|------------------|------------------------|-----|
| | Initially agreed | Agreed after review | | Persistently disagreed | |
| | (n=25) | (n=15) | | (n=31) | |
| | | Initial EUA | EUA after MRI | EUA | MRI |
| Primary track classification | | | | | |
| Nil | 3 | 1 | 0 | 6 | 2 |
| Sinus | 1 | 2 | 0 | 7 | 1 |
| Superficial/submucous | 3 | 1 | 1 | 0 | 0 |
| Intersphincteric | 7 | 0 | 3 | 1 | 4 |
| Transphincteric | 10 | 11 | 11 | 16 | 18 |
| Suprasphincteric | 1 | 1 | 1 | 3 | 1 |
| Extrasphincteric | 0 | 0 | 2 | 1 | 8 |
| Total | 25 | 16 | 18 | 34 | 34 |
| Internal opening and level | | | | | |
| Nil | 4 | 3 | 0 | 13 | 3 |
| Below dentate | 7 | 0 | 0 | 1 | 0 |
| At dentate | 11 | 12 | 13 | 16 | 19 |
| Above dentate | 3 | 1 | 3 | 3 | 4 |
| Rectal | 0 | 0 | 2 | 1 | 8 |
| Total | 25 | 16 | 18 | 34 | 34 |
| Abscess | | | | | |
| Superficial/submucous | 2 | 0 | 0 | 3 | 1 |
| Intersphincteric | 2 | 2 | 3 | 1 | 1 |
| Ischiorectal | 5 | 1 | 9 | 7 | 12 |
| Supralevator | 1 | 4 | 5 | 3 | 2 |
| Total | 10 | 7 | 17 | 14 | 16 |
| Horseshoe | | | | | |
| Intersphincteric | 0 | 0 | 3 | 1 | 6 |
| Ischiorectal | 2 | 2 | 3 | 9 | 4 |
| Supralevator | 0 | 0 | 1 | 1 | 2 |
| Total | 2 | 2 | 7 | 11 | 12 |

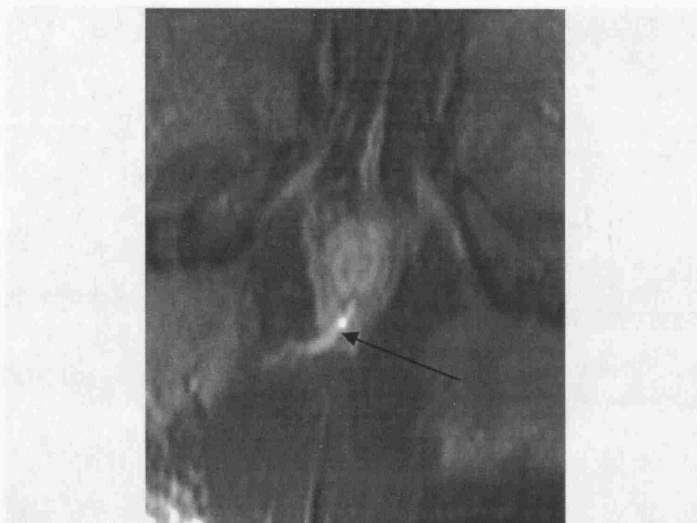


Figure 21: MRI in recurrent fistula. MRI and EUA agree.

42 year old man from Group A in whom MRI and initial EUA had both suggested a transsphincteric fistula with an internal opening at 6 o'clock (arrow). Fistulotomy was performed and the fistula subsequently healed.

Three patients had Crohn's disease. On follow-up, two (13.3%) patients in this group needed further unplanned surgery; extended drainage of a known intersphincteric extension and fistulotomy of a new transsphincteric track that developed at 6 months in a second patient who had been discharged after his intersphincteric fistula had healed. Thus, the latter was the only wholly unpredictable recurrence from Groups A and B combined.



Figure 22: MRI in recurrent fistula: Therapeutic impact of MRI.

39-year-old man from Group B in whom MRI revealed a deep ishiorectal extension with a left-sided supralelevator extension (arrow), unsuspected at initial EUA. There was no external opening. Blind incision was made at review EUA using the MRI for guidance and the extension identified and drained, allowing resolution of sepsis.

Group C: Persistent disagreement between MRI and EUA.

There were 31 (43.7%) patients in whom ultimate disagreement persisted between MRI and surgical findings (Table 3). This related to minor differences in fistula classification in four (for example high transsphincteric versus suprasphincteric), major differences in four (for example extrasphincteric versus transsphincteric) and discrepancies related to extension location and description in five. An abscess/ horseshoe extension was found at 'initial' EUA in six subjects that was absent on MRI. MRI also missed two fistulas; a high transsphincteric track in a patient with a co-existing extrasphincteric fistula, and an intersphincteric track with a seton in situ. No 'review' EUA was judged necessary in any of these patients. MRI suggested a track and internal opening in 13 subjects, 7 of whom

“initial” EUA had classified as a sinus; no external opening had been found in the remaining 6. In seven subjects, MRI suggested an extension apparently missed at ‘initial’ EUA. The operating surgeon elected not to perform a ‘review’ EUA in any of these cases because of their confidence in their operative findings at ‘initial’ EUA. Five patients from this group had Crohn’s disease. Overall MRI suggested more fistulas, more and higher internal openings and more extensions than did EUA in this group (Table 3, page 64).

On follow-up, 16 (51.6%) of patients from Group C needed further unplanned surgery. Surgery confirmed sepsis at the site initially predicted by MRI in all 16 (Figure 23, page 96); eight developed a fistula at the site predicted by MRI; an abscess/horseshoe extension was found at the site predicted by MRI in four (three of which were missed at EUA and one that was believed to be ischiorectal at EUA but which MRI and further surgery confirmed as intersphincteric); both a fistula and associated extension developed at the site predicted by MRI in three, and one had a non-healing fistula that MRI had correctly classified as high transsphincteric.

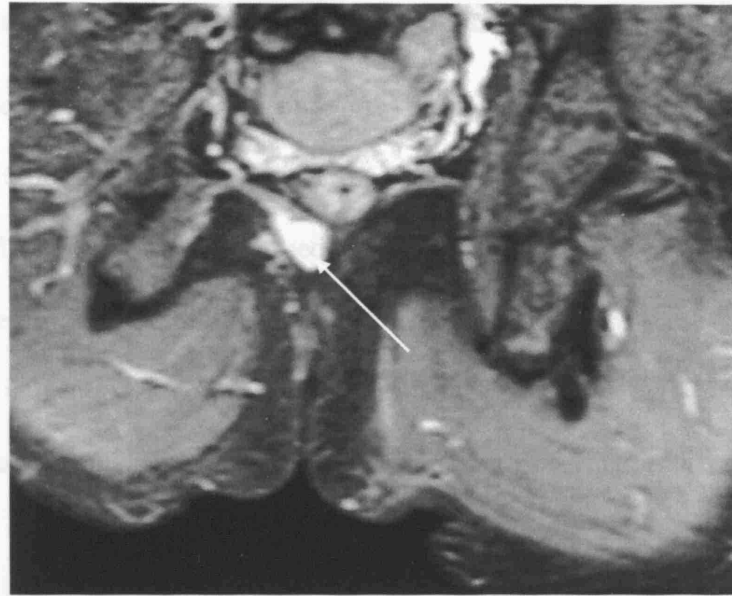


Figure 23: Surgeon ignored MRI findings.

43 year old man from Group C who had 15 previous operations for sepsis. MRI revealed a deep ischiorectal abscess (arrow). There was no external opening. The operating surgeon elected not to perform a review EUA. The patient represented at three months and subsequent EUA revealed a collection at the site predicted by MRI, which was drained.

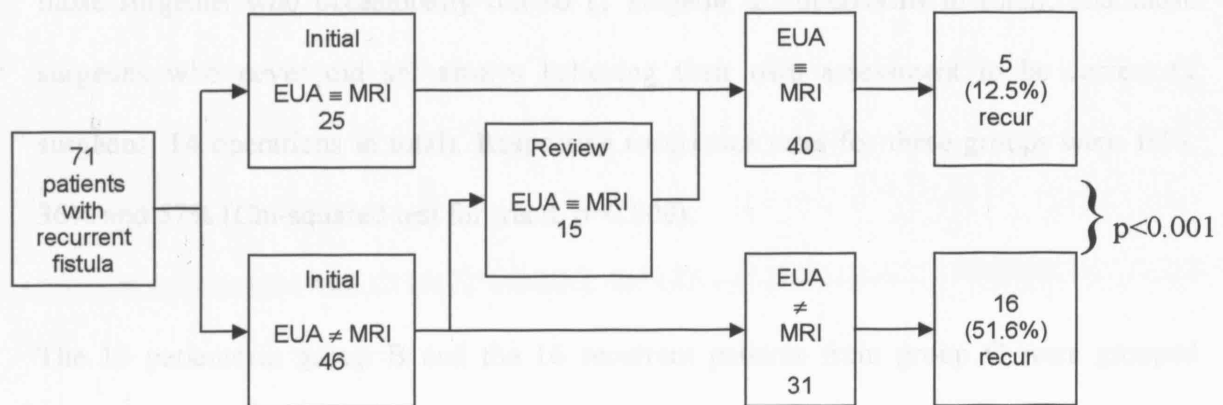


Figure 24: Frequency of postoperative recurrence related to operative agreement with MRI.

Clinical outcome related to surgical attitude to MRI

The clinical recurrence rates in groups A, B and C were 12%, 13.3% and 51.6% respectively ($p=0.001$). Overall, there were 5 (12.5%) recurrences from the 40 patients in whom MRI and EUA ultimately agreed compared with 16 (51.6%) from the 31 where disagreement persisted ($p=0.0005$) (Figure 24, page 98). There were significantly more simple fistulas in group A compared to groups B ($p=0.034$) and C ($p=0.014$) but no difference between groups B and C ($p=1.0$) despite their differing recurrence rates.

In order to assess the effect of surgical attitude to MRI findings on outcome, all surgeons who had experienced discrepancy between MRI and the 'initial' EUA, and who subsequently had patients who recurred on follow-up were identified; these were 6 Consultant surgeons. They were then grouped on the basis of their reaction to the discrepancy between their assessment and MRI; those surgeons who always performed a 'review' EUA to check their findings against the MRI (3 surgeons, 25 operations in total); those surgeons who occasionally did so (1 surgeon, 25 operations in total); and those surgeons who never did so, always believing their own assessment to be correct (2 surgeons, 14 operations in total). Respective recurrence rates for these groups were 16%, 36% and 57% (Chi-squared test for trend, $p=0.008$).

The 15 patients in group B and the 16 recurrent patients from group C were grouped together to define those 31 individuals where MRI was objectively needed (in retrospect), and compared to the 40 where it was not (i.e. 25 group A patients and 15 non-recurrent group C). Before imaging was revealed, surgeons felt MRI was likely to be helpful in 24

from the 31 (77.4%) where MRI was judged objectively needed versus 19 of the 40 (47.5%) where it was not ($p=0.014$). After surgery, including any 'review' EUA, surgeons felt imaging had been useful in 19 of 31 (61.3%) versus 12 of 40 (30%) respectively ($p=0.015$). Median scores for surgical confidence were 8 (range 1-10) versus 8 (range 6-10) respectively ($p=0.027$). There was no significant difference in confidence scores between those surgeons who always, occasionally, or never acted on discrepant MRI findings ($p = 0.770$, ANOVA).

Discussion

Whilst a study of 56 patients found that MRI altered surgical approach in 12 (21%) (Beet-Tan et al. 2001), there has been surprisingly little work relating this to clinical outcome. Indeed, one study of relatively simple fistulas showed no benefit (Schofield et al. 1997). However, although it seems sensible to assume that finding and acting upon previously undetected tracks and extensions will prevent recurrence, most fistulas are easy to treat and will not recur in any event. Because of this, significant therapeutic impact and a consequent positive effect on outcome are most likely to be found in those with recurrent disease.

Studies that measure the effect of imaging on outcome are notoriously difficult, not least because seemingly beneficial imaging is rapidly adopted before proper assessment can be made (Dixon, 1997). Indeed, we had intended to perform a randomised controlled trial but were prevented from doing so by our hospital ethical committee who felt patients should not be denied MRI, despite the lack of randomised evidence supporting its use in this

setting. The pre- and post-intervention design that we ultimately adopted is a well-validated alternative to a randomised design, which measures the therapeutic effect of imaging (Dixon, 1997). Also, because we used 11 different surgeons, we were still able to investigate the effect of intervention on the basis of MRI findings because surgical attitude to imaging was variable.

To our knowledge, this is the first study to demonstrate that fistula surgery influenced by MRI findings can reduce subsequent clinical recurrence. There was no significant difference in fistula complexity between groups B and C yet the recurrence rate in group B, where surgery and MRI ultimately agreed after further exploration, was approximately one-quarter of that found in Group C. Indeed, the recurrence rate in groups B was essentially the same as those in Group A, where 'initial' EUA and MRI agreed without the need for further surgical exploration. Furthermore, subsequent clinical recurrence in all 16 patients from group C was surgically unexpected and at the site initially predicted by MRI whereas groups A and B yielded only one recurrence due to a wholly 'new and unanticipated' finding on follow-up. The major difference between groups B and C was the belief and enthusiasm with which surgeons acted upon discordant MRI findings. Surgeons who always acted upon imaging discrepancy had a recurrence rate that was approximately one quarter that of those who never acted (16% vs. 57%), a highly significant difference.

The reasons why some surgeons chose not to act upon discrepant MRI findings are probably complex. Self-belief in digital examination and surgical exploration varies, so that even when confronted by a seemingly unambiguous scan, re-exploration was sometimes deemed unnecessary by the operating surgeon. Also, assessment of recurrent fistulas is

particularly difficult; scarring impairs palpation of underlying tracks and extensions and, alternatively, may mimic underlying disease. Furthermore, where there was no external opening, some surgeons were understandably reluctant to incise apparently normal tissue in order to reach an abscess or extension that was impalpable but suggested by MRI. In contrast, others appeared to have a stronger personal conviction that MRI was correct. A similar situation arose when MRI suggested the location of an internal opening that was not clinically obvious to the operating surgeon. Surgeons in group B incised at the site indicated by MRI whilst those in group C did not. The finding of a sinus at EUA but fistula at MRI was one of the strongest predictors of recurrence, invariably with an internal opening at the site predicted by MRI. In practical terms, finding an internal opening via MRI allows fistulotomy or seton treatment. MRI evidence of an undetected extension or track was also a strong predictor of recurrence. Changes in classification prompted by MRI were also useful. For example, setons were avoided and fistulotomy performed where MRI found that a supposed transsphincteric fistula was actually intersphincteric and vice versa. Also, extensions ultimately found to be supralelevator rather than ischiorectal could be appropriately drained. It is interesting to note that surgeons accurately perceived significantly more need for MRI in those patients where it retrospectively proved useful, before and after findings were revealed in theatre. Moreover, although surgical confidence was significantly lower in those patients where MRI was needed, the absolute value was relatively high; median score 8.

However, MRI is not necessarily better than EUA; a combination of both is likely to be required for wholly accurate assessment. Indeed, MRI missed clinically important extensions and fistulas, notably because they were gas filled, superficial or contained a

seton (which drains the fistula and thus diminishes the signal returned from inflammatory material). It is also clear that MRI has some difficulty locating the precise level of the internal opening, primarily because the dentate line is not visualised as a discrete anatomical structure. A common cause of persistent discordance was an MRI prediction of a high internal opening, usually extrasphincteric, in the face of an EUA that suggested a lower communication. The improved spatial resolution possible with a dedicated endoanal coil (Stoker et al., 1996) does not seem to more accurately define the internal opening level and field-of-view limitations may miss distant extensions and endoanal coils cannot therefore be recommended in isolation (deSouza et al., 1998). Also, the MRI technique used for this study is widely available, simple, needs no special patient preparation and should be easily adoptable by centres performing fistula surgery.

In summary, all patients with recurrent fistula-in-ano should have preoperative MRI, which has considerable therapeutic impact in this group. Persistent discrepancy between MRI and EUA strongly predicts further recurrence, and surgeons ignoring additional information provided by MRI have recurrence rates over 50%. Surgery guided by MRI can reduce further recurrence by approximately 75%.

Chapter 4:

Magnetic Resonance Imaging for Primary Fistula-In-Ano

Introduction

Whilst MRI-guided surgery has undoubted benefit in recurrent fistula-in-ano (see Chapter 3), it is unknown whether this strategy prevents recurrence in patients initially presenting with primary fistulas believed to be simple. This prospective study aimed to determine the therapeutic effect of pre-operative MRI in patients presenting with primary fistula-in-ano and to investigate the consequences of MRI-guided surgery on clinical outcome.

Methods

Patients

30 consecutive patients (19 men; median age = 37 years, range 17 to 61) with primary cryptoglandular fistula-in-ano were recruited prospectively. To avoid selection bias, all patients without history of previous fistula surgery were eligible, although nine underwent perianal abscess drainage before their referral. Nine were tertiary referrals despite having seemingly simple fistulas. In outpatients, the assessing clinician indicated whether they would have requested MRI outside the context of a clinical trial.

Procedures

All patients underwent MRI at a median of 4 (range 0 to 79) days preoperatively, using the protocol described in Chapter 3. A pre- and post- intervention observational study design as

described in Chapter 3 was employed. An experienced consultant gastrointestinal radiologist (SH, CIB), blinded to clinical detail, supervised scanning, then recorded the scan findings using a fistula classification sheet (Lunniss et al., 1994; Thomson & Ross, 1989) using a methodology identical to that described in Chapter 3. This was sealed in an envelope and taken to the subsequent EUA as described in Chapter 3. Surgery was performed by one of 13 experienced surgeons (6 consultants in 23 patients, 7 year six trainees in 7). The surgeon performed and documented 'initial' EUA assessment (see Chapter 3), and stated whether he/she believed that MRI was likely to be helpful. MR imaging review, additional surgery in light of MRI findings and documentation of the 'review' EUA assessment, postoperative care and definition of recurrence was as described in Chapter 3. Any recurrence was documented and findings at any subsequent operations noted. Median follow-up was 12 months (range, 5 to 39).

MRI and EUA assessments were compared with respect to primary and secondary track classification and internal opening location. Categorical frequencies were analysed using Fishers exact test. Analysis was performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, UK). Statistical significance was assigned at the 5% level.

Results

'Initial' EUA and MRI findings agreed in 15 patients (50%); 14 had sepsis, of which 13 were fistulas (Table 4 (page 110), Figure 25 (page 107)): three patients had secondary extensions. MRI findings precipitated additional surgery in 3 further cases, leading to

ultimate agreement between MRI and EUA (Table 4 (page 110), Figure 26 (page 108)). Thus the therapeutic impact of MRI was 10%. MRI revealed an internal opening in two patients initially thought to have a sinus, allowing definitive treatment, and prevented further exploration in a third where a horseshoe suspected clinically was absent on imaging.



Figure 25: Primary fistula: MRI and Surgery agree

Axial STIR sequence MRI at mid anal canal level of a 42 year old man, in whom MRI and initial EUA had both suggested a trans-sphincteric fistula with an internal opening at 6 o'clock (arrow). Fistulotomy was performed and the fistula subsequently healed.

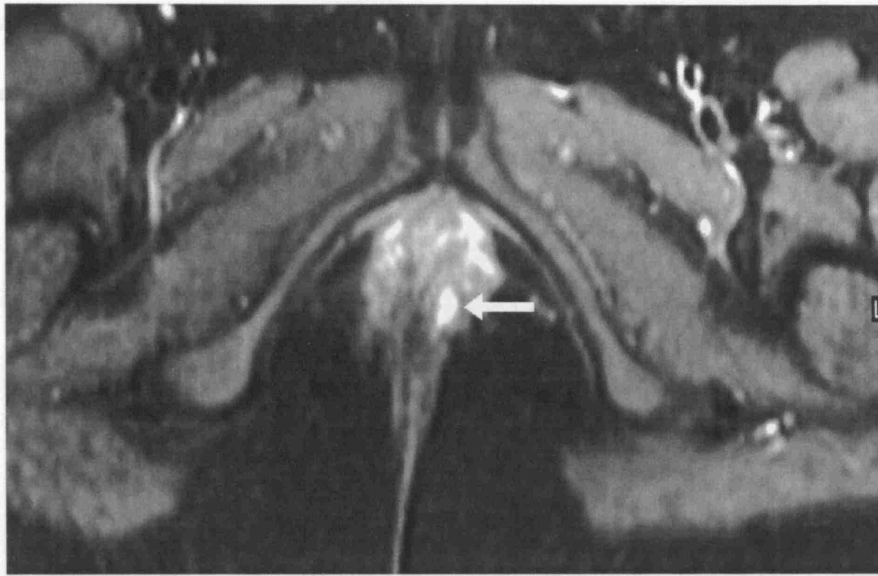


Figure 26: Primary fistula: MRI influences surgery

Axial STIR sequence MRI at mid anal canal level in a 17 year old woman. The surgeon, diagnosing a sinus following initial EUA, used the MRI for guidance that confirmed an anterior internal opening and intersphincteric sepsis (white arrow). A seton was subsequently placed through a trans-sphincteric fistula.

Disagreement persisted between MRI and EUA assessments in 12 patients (40%)(Table 4). In nine, this related to minor differences in fistula classification (Figure 27, page 109); for example high trans-sphincteric versus supra-sphincteric. In one of these, discrepancy also related to extension location, and in another MRI missed an ischiorectal extension. In another two patients disagreement related to a major difference in classification; in one MRI suggested an extra-sphincteric fistula whereas EUA revealed a trans-sphincteric track opening at the anorectal junction, and in another MRI suggested a supra-sphincteric fistula with a supralelevator extension, although EUA found the primary track was intersphincteric. In a further patient, MRI missed a superficial sinus that was easily found at 'initial' EUA. No 'review' EUA was deemed necessary following disclosure of MRI findings in any of

these 12, with discrepancies judged as semantic variations in fistula classification that did not affect operative approach.

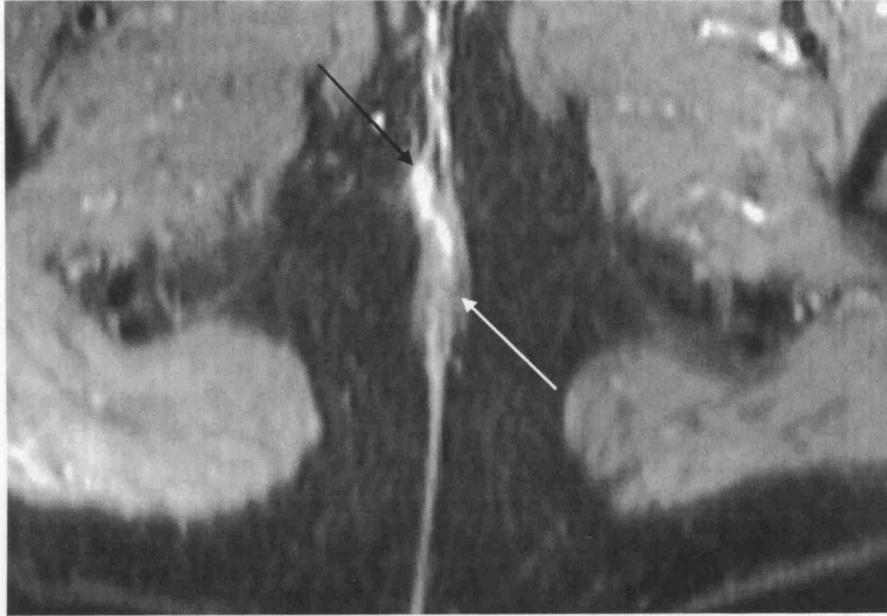


Figure 27: Primary fistula: MRI and surgery disagree

Axial STIR sequence MRI at the level of the subcutaneous external sphincter (white arrow), of a 47 year old man who underwent fistulotomy of a trans-sphincteric track (black arrow) at EUA, which had been misclassified as superficial on MRI. The surgeon did not need to perform a review EUA, and the patient subsequently healed on follow-up.

Table 4: Comparison of EUA and MRI findings in 30 patients

| | Initially agreed (n=15) | | Agreed after further surgery (n=3) | | Persistently disagreed (n=12) | |
|-------------------------------------|-----------------------------------|----|------------------------------------|---------------------|-------------------------------|--------------|
| | Findings at MRI and 'initial' EUA | | Initial EUA findings | Review EUA findings | MRI findings | EUA findings |
| Primary track classification | Nil | 1 | 0 | 0 | 1 | 0 |
| | Sinus | 1 | 2 | 0 | 0 | 1 |
| | Superficial/submucous | 4 | 0 | 1 | 1 | 0 |
| | Intersphincteric | 5 | 1 | 1 | 7 | 1 |
| | Trans-sphincteric | 4 | 0 | 1 | 1 | 9 |
| | Suprasphincteric | 0 | 0 | 0 | 1 | 1 |
| | Extrasphincteric | 0 | 0 | 0 | 1 | 0 |
| | Total | 15 | 3 | 3 | 12 | 12 |
| Internal opening and level | Nil | 2 | 2 | 0 | 1 | 1 |
| | Below dentate | 8 | 0 | 1 | 2 | 1 |
| | At dentate | 4 | 1 | 2 | 7 | 9 |
| | Above dentate | 1 | 0 | 0 | 1 | 1 |
| | Rectal | 0 | 0 | 0 | 1 | 0 |
| | Total | 15 | 3 | 3 | 12 | 12 |
| Abscess | Superficial/submucous | 1 | 1 | 1 | 1 | 0 |
| | Intersphincteric | 1 | 0 | 0 | 0 | 0 |
| | Ischiorectal | 1 | 0 | 0 | 1 | 2 |
| | Suprlevator | 0 | 0 | 0 | 1 | 1 |
| | Total | 3 | 1 | 1 | 3 | 3 |
| Horseshoe | Intersphincteric | 0 | 1 | 0 | 1 | 0 |
| | Ischiorectal | 0 | 0 | 0 | 0 | 1 |
| | Suprlevator | 0 | 0 | 0 | 0 | 0 |
| | Total | 0 | 1 | 0 | 1 | 1 |

In outpatients, surgeons stated they would have routinely requested MRI in 14 of the 30 (46.7%) patients, including all 3 in whom MRI subsequently altered surgical approach. There was no significant difference between consultants and trainees with respect to this (5/14 assessments versus 9/16 respectively, $p=0.299$). After initial EUA, surgeons felt MRI findings would be helpful in 11 (36.7%) cases, again including the 3 where MRI altered management. Again, there was no difference between consultants or trainees (8/23 versus 3/7 respectively; $p=1.000$). Overall, surgeons found imaging useful in 14 (46.7%) patients, including the 3 in whom MRI had therapeutic impact, again with no difference between consultants or trainees (10/23 versus 4/7 respectively; $p=0.675$).

Only one patient relapsed, a subject from the group of three in whom MRI had precipitated further surgery. In this instance further unplanned surgery was for skin bridging rather than any new sepsis, and so was not wholly unanticipated.

Discussion

MRI is known to be useful in complex fistula-in-ano (see chapter 3) but the role of MRI in seemingly simple fistulas is less clear. A study of 27 patients, where MRI was revealed peri-operatively, included 25 with primary fistulas, and MRI precipitated additional surgery in only one patient (Schofield et al., 1997). However, the authors admitted that their radiologist was initially unfamiliar with fistula MRI and concluded that the considerable learning curve associated with the technique probably prejudiced their results. This present study determined the therapeutic effect of MRI in patients with primary fistula-in-ano using experienced radiologists, and documented the cause

for any relapse, using a well-validated and previously applied study design (see chapter 3).

Fistula recurrence is often due to sepsis missed at EUA (Seow & Phillips, 1991). Extensions occur in approximately 10-15% of cases (Marks & Ritchie, 1977), and are more prevalent in recurrent or Crohn's fistulas. This study has confirmed their relative scarcity in consecutive patients with primary fistulas. Nevertheless, imaging influenced surgery in 10%, a figure not too distant from the 21% established in the group of 71 subjects with recurrent disease (see chapter 3). However, in that study over 50% of patients in whom there was persistent disagreement between MRI and EUA relapsed (see chapter 3). Most disagreement related to the presence of MRI identified sepsis, unlike the present study where disagreement was predominantly due to semantic variations in classification.

The two patients in this study believed to have a sinus at EUA, but found to have a fistula following disclosure of the MRI findings in theatre, would probably have recurred in the absence of imaging (see chapter 3). Indeed, there was no relapse due to any new sepsis in the present study, with further unplanned surgery only required to divide skin bridging in one patient; longer-term follow-up could verify this. Whether MRI should be performed in all patients with primary fistula-in-ano in return for a therapeutic impact of 10% is a matter for local debate in the face of cost-containment since MRI is a target for cost control (Halligan & Bartram, 1998). However, scanning costs for this study totalled £2100, substantially less than the estimated cost of £2844 to operatively treat a single recurrence, not withstanding the cost to the patient in terms of personal suffering and lost employment. A cheaper alternative may be anal

endosonography, which, although initially disappointing in fistula-in-ano (Cheon et al, 1991), shows greater promise in studies using higher frequency transducers (Schwartz et al., 2001). Further research undertaken in this area is presented in chapter 5.

Although the therapeutic impact of MRI was 10%, surgeons in 11 cases perceived a need for imaging before the results were revealed and felt it was useful in retrospect in 14 cases. This was most likely due to increased diagnostic confidence, which may occur without any formal change in operative approach or fistula classification. MRI was not always correct in the present study. However, disagreement was usually clinically insignificant, and again related to imprecise localisation of the height of the internal opening.

In summary, in experienced hands MRI has a therapeutic impact of 10% for primary fistula-in-ano and precipitates surgery likely to reduce recurrence in a small, though important, proportion of patients.

Chapter 5:

A prospective evaluation of clinical examination,
endosonography, and magnetic resonance imaging for
preoperative assessment of fistula-in-ano:

Comparison to an outcome derived reference standard.

Introduction

Surgeons have traditionally relied on inspection and digital examination for the initial assessment of fistula-in-ano, prior to EUA, but digital examination may fail to recognize complex fistulas or may classify them incorrectly (Seow-Choen & Nicholls, 1992; ASCRS, 1996a). It is now well established that pre-operative imaging, in particular MRI (Chapters 3 and 4), can alert surgeons to infection that would otherwise be missed.

However, there are many health-care systems worldwide where access to MRI is restricted. It is also relatively expensive. Fistulography, although less expensive and more readily available, is inaccurate (Kuijpers & Schulpen, 1985) and assessment by CT scanning is similarly unhelpful (Halligan, 1998). AES is a simple inexpensive alternative that may be used either in an outpatient setting, or in the operating suite. AES is widely used for imaging the anal sphincter complex (Law & Bartram, 1989), notably in incontinent patients (Sultan et al., 1993). While pre-operative investigation of fistula-in-ano was one of the earliest applications of AES (Law et al., 1989), its benefit for this indication remains uncertain; some authors have found it very useful (Deen et al., 1994; Lindsey et al., 2002) while others have found it no better than digital examination (Choen et al., 1991), and direct comparisons with MRI have found it both superior (Orsoni et al., 1999), equivalent (Gustafsson et al., 2001; Schwartz et al., 2001), and inferior (Hussain et al., 1996). Ultrasound probe technology has improved dramatically in recent years (Frudinger et al., 2002) and the role of AES now needs further definition in the light of these developments and in relation to the simultaneous advances made by MRI. Thus, the purpose of this study was to prospectively evaluate

the relative accuracy of digital examination, AES, and MRI for the pre-operative assessment of fistula-in-ano by comparison with an outcome-derived reference standard.

Methods

Patients

108 consecutive patients with suspected fistula-in-ano were prospectively recruited from outpatients. To avoid selection bias, all patients with a possible fistula were eligible for inclusion; irrespective of whether the surgeon felt preoperative imaging was clinically necessary. Three female patients declined AES or could not undergo full clinical evaluation due to severe anal pain, and one female patient could not tolerate MRI because of claustrophobia, leaving a study population of 104. There were 74 men, median age 42.5 years, range 21 to 66 years; and 30 women, median age 42 years, range 17 to 61 years. There was no significant difference in age between men and women ($p=0.301$).

Of these 104, 28 (27%) were presenting with primary fistula-in-ano (7 of whom had previously undergone perianal abscess drainage) while 76 (73%) were recurrent. Patients with recurrent disease had undergone a median of 3 operations (range 1 to 19) prior to referral. There were 9 (8.7%) patients with known Crohn's disease overall, all from the recurrent group. All other patients were believed to have cryptoglandular fistula-in-ano (Parks, Gordon and Hardcastle, 1976). Ninety of the 104 were enrolled as part of the trials described in chapters 3 ($n=63$) and 4 ($n=27$), and the remaining 14

patients were recruited separately with EUA to be performed with the MRI report and films available from the outset.

Clinical assessment

Clinical evaluation in the outpatient department was performed by one of 8 consultant colorectal surgeons (range of colorectal experience 9 – 30 years) or 15 senior colorectal trainees in their last year of subspecialty training (range of colorectal experience, 3 – 6 years). Senior trainees had been trained by the consultant surgeons and had subsequently performed examinations on a regular basis. Trainee assessment in this study was performed unsupervised.

Clinical assessment was at a mean of 79 days prior to surgery (standard deviation 68.1 days, range same day to 405 days) and consisted of a full history and examination, with the benefit of hospital notes and referral letters. Abdominal examination was followed by anorectal assessment with patients in the left lateral decubitus position. Inspection and palpation of the perineum was combined with digital examination of the anorectum and proctosigmoidoscopy in order to determine the course of any fistula track and any associated extensions. Fistula probes were not employed for fear of creating additional tracks.

On the basis of this assessment the clinician independently completed a fistula classification sheet (as in Chapter 3). Using this sheet, the primary track of any fistula, if clinically present, was recorded as intersphincteric, transsphincteric, suprasphincteric or extrasphincteric (Parks, Gordon & Hardcastle, 1976). Superficial fistulas (i.e. those not

thought to actually cross the anal sphincter muscle) were grouped with intersphincteric fistulas as these were sometimes indistinguishable, and both types were always laid open. The internal opening location was recorded with respect to a clock-face, and its level recorded as either anal or rectal. The anatomical location of any abscess or horseshoe extension arising from the primary fistula track was recorded as follows: superficial, intersphincteric, ischiorectal or supralelevator (ASCRS, 1996a; Parks, Gordon & Hardcastle, 1976). Any track appearing blind ending (i.e. where an internal opening could not be defined clinically) was classified as a sinus rather than a fistula.

This outpatient fistula classification sheet was sealed in an envelope for later comparison against an outcome-derived reference standard. All patients underwent subsequent AES and MRI, each blinded to the results of any other assessment.

Anal endosonography

One of two experienced gastrointestinal radiologists (SH, CIB) or two surgical research fellows (GNB, ABW) performed AES. All were experienced in anal endosonography. The radiologists had in excess of 10 years and 6 years experience with the technique respectively at the commencement of study recruitment. The surgical research fellows both had in excess of one years experience, each having been trained by the two radiologists and having subsequently performed examinations on a daily basis for that period. AES performed by research fellows in this study was unsupervised.

Scanning was at a mean of 18 days prior to surgery (standard deviation 36.4 days, range same day to 183 days). A B-K Medical (Herlev, Denmark) scanner type 3535 (69

patients) or 2100 (35 patients) was used. A 10-MHz transducer (type 6004) was used in all cases, attached to a B-K Medical type 1850 rotating endoprobe (Herlev, Denmark). The transducer has a focal length of 5-45mm, an axial resolution of less than 0.05mm, a lateral resolution of 0.5-1mm and a beam thickness of 0.8mm (Frudinger et al., 2002). The transducer was covered with a hard sonolucent plastic cone of 1.7cm in diameter and the assembly was filled with degassed water for acoustic coupling, covered with a lubricated condom, and inserted into the anal canal with patients in the left lateral (male) or prone (female) position (Frudinger et al., 1998). The endoprobe is withdrawn until the “U” sling of puborectalis is visualised. The axial image of the anal canal shows a four-layer pattern (Bartram & Frudinger, 1997). Fistulas were identified using established criteria (Bartram & Buchanan, 2003), namely a hypoechoic track, occasionally containing focal bright echoes representing gas within the fistula. Serial axial images of the anal canal during slow probe withdrawal were taken by the sonologist at two different magnifications and printed on laser film. The sonologist independently recorded their findings on a sheet identical to that used for clinical examination, using the same definitions. The sonologist was blind to the clinical findings in outpatients and was only aware that the patient potentially had a fistula. This sheet was then sealed by the sonologist in an envelope for later comparison against an outcome derived reference standard. All scans were deemed technically adequate and no patient was recalled for further imaging.

MR Imaging

Following AES, all patients underwent MRI on the same day using a previously described and well-validated body (13 patients) or phased array surface-coil (91

patients) protocol, as described in chapter 3. One of the same two gastrointestinal radiologists (SH, CIB) supervised MRI, and scans were allocated such that the radiologist was blind to any findings on prior AES (i.e. AES had been performed by either the non-supervising radiologist or one of the fellows). Again, the radiologist was also unaware of any outpatient findings except that the patients potentially had a fistula. The supervising radiologist independently recorded their MRI findings on a fistula sheet identical to that used for the clinical and AES assessments, again noting their opinion of fistula classification, internal opening, and any associated extensions. The radiologist then sealed this sheet in an envelope, which was to be used subsequently by surgeons and for later comparison against an outcome derived reference standard.

Examination under anaesthetic

EUA was performed as described in chapter 3 by one of 9 colorectal consultant surgeons (range of colorectal experience 9 – 30 years) in 92 patients, or 10 colorectal trainees in their last year of subspecialist training (range of colorectal experience, 3 – 7 years) in 12 patients. Surgical research fellows did not undertake surgery. No attempt was made to allocate patients according to whether the surgeon had performed outpatient clinical assessment. Furthermore, any outpatient clinical assessment previously recorded in the notes was available at the time of surgery, as per usual clinical practice.

Because previous studies have established that EUA alone is imperfect (Lunniss et al. 1994; Hussain et al., 1996; Spencer et al. 1998; Orsoni *et al* 1999; Beets-Tan et al., 2000; Beets-Tan et al., 2001; Gustafsson et al., 2001; Maier et al., 2001; Schwartz et

al., 2001; Buchanan et al., 2002) (chapters 3 & 4)) MRI results were available at the time of EUA in order to maximise the surgeons' chance of detecting fistula tracks and extensions. EUA was performed with the benefit of MRI from the outset in 14 patients, and initially performed blind to the results of MRI in 90 patients, as part of the trials described in chapters 3 (n=63) and 4 (n=27). The operative fistula classification at the end of EUA (i.e. including any additional information from MRI) was independently documented by the operating surgeon on a fistula sheet identical to that used for pre-operative assessments, which was retained, to be used subsequently for the outcome derived reference standard.

Outcome derived reference standard

Because it is well established that fistula recurrence is commonly caused by infection missed at EUA (ASCRS, 1996a; Lunniss et al., 1994; Seow-Choen & Nicholls, 1992; Garcia-Aguilar et al, 1996; Spencer et al., 1998; Chapple et al., 2000) (Chapter 3)) patients were followed up in order to determine clinical outcome and so identify those patients in whom infection had been missed. This procedure was especially important because not all surgeons chose to act on MRI findings that suggested they had missed occult infection during their surgical exploration (chapter 3). Patients were followed-up for a mean period of 23 months (standard deviation 11 months, range 3 to 46 months) and assessed in outpatients, with special attention paid to clinical evidence of fistula healing. Follow-up was undertaken by the surgical team responsible for the patient's care, who at this stage, had available all previous assessments that had been performed (Clinical, MRI, AES and surgical findings). Follow-up was as per normal care; there was no attempt to increase its frequency or duration for the purpose of this study.

Documentation was made of any patients where further unplanned surgery was required because of failure to heal or further recurrence (further surgery was planned in a proportion of patients, for example to lay-open a track following a period of seton drainage, or to remove a seton), together with its nature and findings.

An outcome-derived reference standard fistula classification was determined for each patient recruited, based on MRI, EUA, and clinical outcome, incorporating any fistula or abscess found at any subsequent unplanned surgery. This was an extension of the methodology of Schwartz and co-workers, who found that a combination of at least two modalities was necessary in order to be confident that classification was correct (Shwartz et al., 2001). We felt it important to additionally include assessment of clinical course following surgery because fistula healing is the only definitive assurance that all infection has been identified and treated (ASCRS, 1996a; Seow-Choen & Nicholls, 1992).

The following criteria were used: In 74 patients the fistula classification by MRI and final surgical classification at EUA agreed, and was defined as the outcome-derived reference standard because EUA was followed by complete healing (or control of infection where loose setons were employed) in these patients. In the remaining 30 patients there was some disagreement between MRI and final surgical classification at EUA, and so clinical outcome was used for arbitration as follows: Of these, 13 patients represented with a fistula track or peri-anal abscess at a site initially suggested by MRI but not found at EUA. These patients underwent further unplanned surgery that confirmed infection at the site originally suggested by MRI and so the MRI classification was assumed to be correct. The remaining 17 patients did not need further

unplanned surgery but there was disagreement between MRI findings and EUA. In these patients a consensus reference standard was reached between the study investigators using the methodology of Schwartz and co-workers (2001), supplemented by knowledge that these patients had healed following EUA. Thus, if MRI had suggested an abscess that had not been found at EUA, and healing followed this, then MRI was assumed to have been incorrect. In this way, an outcome-derived reference standard fistula classification was arrived at in all 104 patients.

Statistical analysis

Fistula classification at outpatient clinical and digital assessment, AES, and MRI were compared to the outcome-derived reference standard in order to determine the level of agreement for each individual assessment. Fistula tracks were considered correctly classified when placed into the correct anatomical grouping, extensions (abscess and/or horseshoe) when described in the correct anatomical compartment and quadrant, and internal openings when described within the same quadrant (within two hours on the clock face) and at the correct level (defined as anal or rectal) according to the reference standard. Significant differences in correct classification rates for categorical variables and the *a priori* hypothesis that clinical examination would fare worst and MRI best (with AES intermediate) was examined using the Chi-Squared test statistic for trend, with significance assigned at the 5% level. The accuracy of consultant versus trainee fistula assessment in outpatients was assessed using Fisher's exact test. Agreement between the various categorical assessments and the reference standard was assessed using the unweighted Kappa test statistic, with 95% confidence intervals. Analysis was

performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, Cambridge, UK).

Results

The numbers of fistula tracks correctly classified overall according to the modality used is shown in Table 5. There was a significant linear trend ($p < 0.0001$) in the proportion of tracks correctly classified by each modality, with clinical examination faring worst, AES intermediate, and MRI best, each correctly classifying 61%, 81% and 90% of possible fistulas respectively (Table 5, page 125)(Figure 28, page 128). There was a similar highly significant linear trend for the correct classification of the 48 abscesses ($p < 0.0001$)(Figure 29, page 129), 16 horseshoe extensions ($p = 0.003$), and 99 internal openings ($p < 0.0001$) identified by the reference standard, with clinical examination faring worst and MRI best in each instance. Considering abscess and horseshoe extensions together ($n = 64$), clinical examination only correctly identified 23 (36%), compared to 45 (70%) by AES and 56 (88%) using MRI. Generally, the accuracy of AES lay closer to MRI than digital examination for all features except identification of horseshoe extensions.

Primary Disease

Of the 28 patients with primary disease, the outcome derived reference standard established that 21 had either superficial or intersphincteric fistulas, 4 had trans-sphincteric fistulas, 2 had a sinus, and 1 had no evidence of infection. There was no suprasphincteric or extrasphincteric fistula in this group. Of these 28, clinical

examination correctly classified 17 (61%), AES 23 (82%), and MRI 27 (96%). There were 25 internal openings in this group, all of which were anal and which were correctly identified by clinical examination in 21 (84%), AES in 23 (92%), and MRI in 25 (100%). There were six abscesses in this group of which clinical examination correctly classified five (83%), AES two (33%), and MRI four (67%). No patient in this group had a horseshoe extension.

Table 5: Accuracy of clinical examination, AES, and MRI

Number of correct classifications achieved by clinical examination, AES, and MRI respectively, by comparison with the outcome derived reference standard.

| Feature examined | Patients correctly classified | | | p* |
|-------------------------------|-------------------------------|---------|---------|---------|
| | n (%) | | | |
| | Clinical examination | AES | MRI | |
| Primary tracks (n = 108) | 66 (61) | 87 (81) | 97 (90) | <0.0001 |
| Abscess (n = 48) | 16 (33) | 36 (75) | 41 (85) | <0.0001 |
| Horseshoes (n = 16) | 7 (44) | 9 (56) | 15 (94) | 0.003 |
| Internal openings (n = 99) | 77 (78) | 90 (91) | 96 (97) | <0.0001 |

*Chi-squared with linear trend

Table 6: Agreement for primary track classification:

Agreement between clinical examination, AES, MRI, and the outcome derived reference standard for correct classification of the primary fistula tract in 104 patients (four patients had two fistulas). Numbers in bold represent absolute agreement

Classification by outcome derived reference standard

| Clinical evaluation | No infection | Sinus | Superficial or intersphincteric | Transsphincteric | Suprasphincteric | Extrasphincteric | Total | Kappa (95% C.I.) |
|----------------------------------|--------------|-------|---------------------------------|------------------|------------------|------------------|-------|------------------|
| | | | | | | | | |
| Clinical evaluation | | | | | | | | |
| No infection | 0 | 0 | 4 | 3 | 0 | 3 | 10 | |
| Sinus | 0 | 2 | 1 | 3 | 0 | 0 | 6 | |
| Superficial or inter-sphincteric | 1 | 1 | 21 | 4 | 1 | 1 | 29 | |
| Trans-sphincteric | 3 | 2 | 11 | 42 | 1 | 0 | 59 | |
| Supra-sphincteric | 0 | 0 | 1 | 1 | 1 | 0 | 3 | |
| Extra-sphincteric | 0 | 0 | 0 | 1 | 0 | 0 | 1 | |
| Total | 4 | 5 | 38 | 54 | 3 | 4 | 108 | 0.38 (0.25-0.50) |
| AES | | | | | | | | |
| No infection | 2 | 1 | 3 | 0 | 0 | 2 | 8 | |
| Sinus | 1 | 2 | 1 | 0 | 0 | 1 | 5 | |
| Superficial or inter-sphincteric | 0 | 0 | 30 | 2 | 0 | 0 | 32 | |
| Trans-sphincteric | 1 | 2 | 4 | 51 | 2 | 0 | 60 | |
| Supra-sphincteric | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| Extra-sphincteric | 0 | 0 | 0 | 1 | 0 | 1 | 2 | |
| Total | 4 | 5 | 38 | 54 | 3 | 4 | 108 | 0.68 (0.55-0.81) |
| MRI | | | | | | | | |
| No infection | 4 | 1 | 1 | 1 | 0 | 0 | 7 | |
| Sinus | 0 | 3 | 0 | 0 | 0 | 0 | 3 | |
| Superficial or inter-sphincteric | 0 | 0 | 36 | 1 | 0 | 0 | 37 | |
| Trans-sphincteric | 0 | 1 | 1 | 49 | 1 | 0 | 52 | |
| Supra-sphincteric | 0 | 0 | 0 | 0 | 1 | 0 | 1 | |
| Extra-sphincteric | 0 | 0 | 0 | 3 | 1 | 4 | 8 | |
| Total | 4 | 5 | 38 | 54 | 3 | 4 | 108 | 0.84 (0.71-0.97) |

Table 7: Agreement for secondary tracks:

Agreement between clinical examination, AES, MRI, and the outcome derived reference standard for correct identification and localization of extensions, including horseshoe extensions, in 104 patients. Numbers in bold represent absolute agreement

| | Outcome derived reference standard | | | | | | | | | |
|----------------------------|------------------------------------|----|-----|-----|-----|-----|-----|-----|-------|---------------------|
| | Nil | SE | ISE | ISH | IRE | IRH | SLE | SLH | Total | Kappa (95% C.I.) |
| Clinical evaluation | | | | | | | | | | |
| Nil | 36 | 1 | 2 | 3 | 14 | 2 | 2 | 1 | 61 | |
| SE | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | |
| ISE | 3 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 5 | |
| ISH | 2 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 4 | |
| IRE | 2 | 1 | 0 | 0 | 9 | 0 | 2 | 0 | 14 | |
| IRH | 6 | 1 | 0 | 1 | 3 | 6 | 0 | 2 | 19 | |
| SLE | 2 | 2 | 1 | 0 | 1 | 0 | 4 | 0 | 10 | |
| SLH | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.29 |
| Total | 55 | 7 | 4 | 5 | 29 | 8 | 8 | 3 | 119 | (0.20-0.38) |
| AES | | | | | | | | | | |
| Nil | 44 | 3 | 3 | 2 | 2 | 2 | 2 | 0 | 58 | |
| SE | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | |
| ISE | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 5 | |
| ISH | 1 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 4 | |
| IRE | 3 | 1 | 0 | 0 | 27 | 0 | 0 | 0 | 31 | |
| IRH | 3 | 0 | 0 | 1 | 0 | 5 | 0 | 1 | 10 | |
| SLE | 1 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 7 | |
| SLH | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0.64 |
| Total | 55 | 7 | 4 | 5 | 29 | 8 | 8 | 3 | 119 | (0.54-0.74) |
| MRI | | | | | | | | | | |
| Nil | 53 | 2 | 0 | 0 | 2 | 0 | 3 | 0 | 60 | |
| SE | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | |
| ISE | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 4 | |
| ISH | 1 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 6 | |
| IRE | 0 | 0 | 0 | 0 | 27 | 1 | 0 | 0 | 28 | |
| IRH | 1 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 8 | |
| SLE | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 5 | |
| SLH | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 0.88 |
| Total | 55 | 7 | 4 | 5 | 29 | 8 | 8 | 3 | 119 | (0.78-0.98) |

SE = Superficial extension

ISE = Intersphincteric extension

ISH = Intersphincteric Horseshoe

IRE = Ischiorectal extension

IRH = Ischiorectal Horseshoe

SLE = Suprlevator extension

SLH = Suprlevator Horseshoe

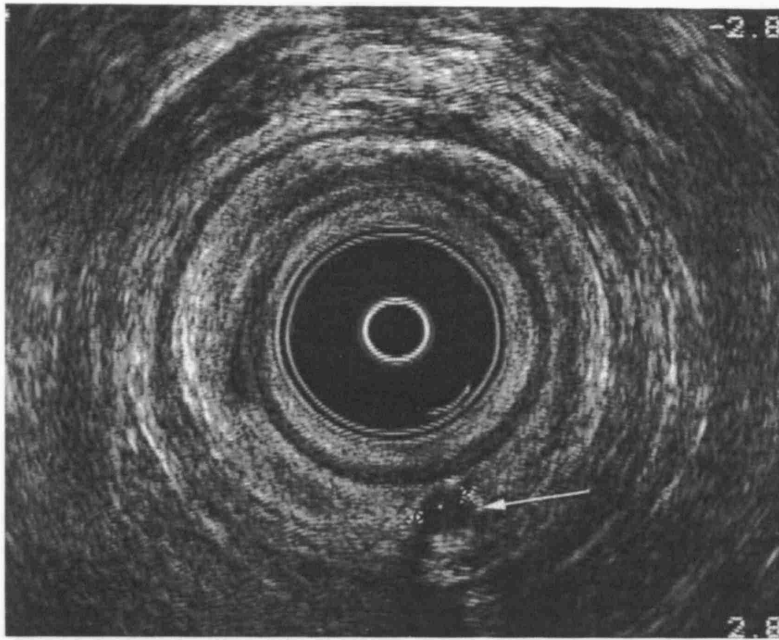


Figure 28: AES of intersphincteric fistula.

56 year-old man, axial AES (10-MHz transducer) at mid anal canal level. Digital examination as an outpatient had suggested infection did not enter the sphincter but anal endosonography revealed an intersphincteric track (arrow), diagnosing an intersphincteric fistula. This was confirmed by the outcome-derived reference standard.

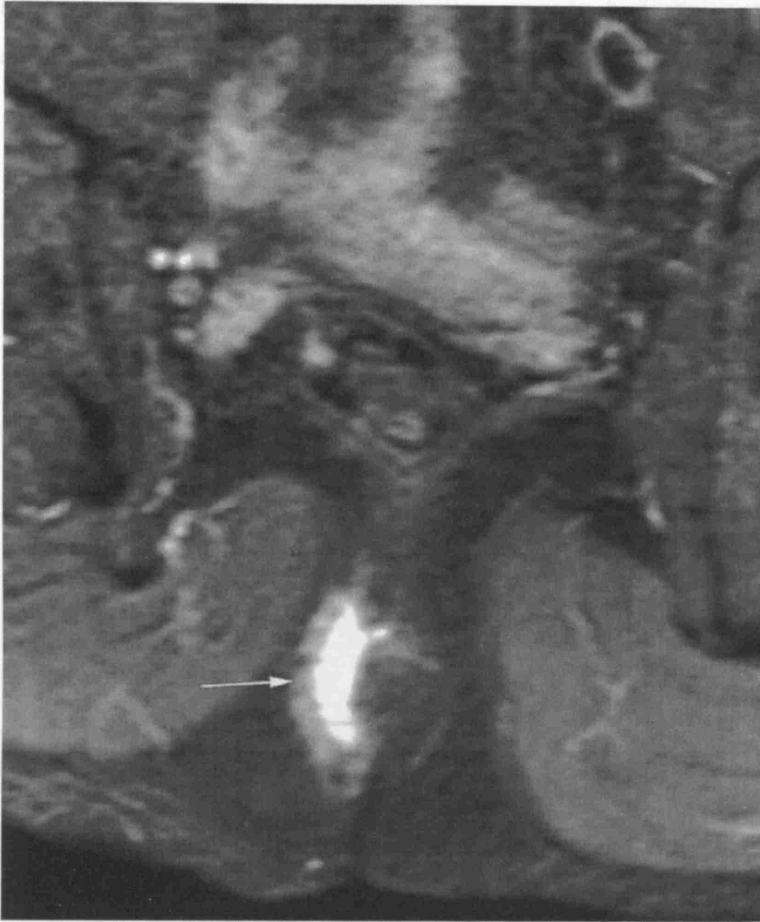


Figure 29: MRI shows ischiorectal abscess missed on AES

42 year-old man, coronal body-coil MRI STIR image (TR/TE (msec), 1500/15; field-of-view 375 mm; 256 x 256 matrix; 4mm slice thickness; 1mm interslice gap; 4 excitations) in whom both digital examination and AES had diagnosed a transsphincteric fistula. MRI additionally revealed an unsuspected ischiorectal abscess (arrow), which was confirmed by the outcome-derived reference standard.

Figure 30: AES and MRI agree.

54 year-old man with recurrent perianal infection, in which digital examination as an outpatient had suggested an extrasphincteric fistula with a rectal opening.

**Figure 30a**

A, axial AES (10-MHz transducer) at mid anal canal level suggests a transsphincteric track (solid arrow) and an ischiorectal extension (dashed arrows).



Figure 30b

B; same patient as 3A. Axial MRI (TR/TE, 1500/15 (msec); field-of-view 375 mm; 256 x 256 matrix; 4mm slice thickness; 1mm interslice gap; 4 excitations) also confirmed a transsphincteric fistula (arrow) with an ischiorectal extension (dashed arrows). These findings were confirmed by the outcome-derived reference standard, showing AES and MRI to be correct.

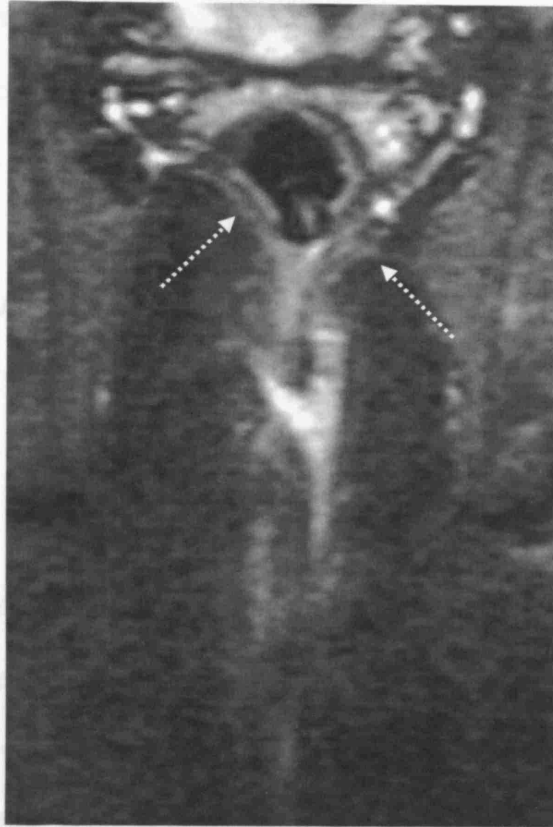


Figure 30c

C; Coronal MR images clearly demonstrate that infection lies beneath the levator plate (arrows).

Recurrent Disease

Of the 76 patients with recurrent disease, the outcome derived reference standard established 17 superficial or intersphincteric fistulas, 50 trans-sphincteric fistulas, 3 suprasphincteric fistulas, and 4 extrasphincteric fistulas. There were 3 patients with a sinus and 3 with no evidence of infection. Four patients had two tracks each, resulting in 80 possible classifications in this group overall. Of these 80, clinical examination correctly classified 49 (61%), AES 64 (80%), and MRI 70 (88%). There were 74 internal openings that were correctly identified by clinical examination in 56 (76%), AES in 67 (91%), and MR imaging in 71 (96%). Four of these internal openings were rectal, all of which were correctly identified using MRI but in only one case each by

both clinical examination and AES. There were 42 abscesses in this group, 11 (26%) of which were correctly classified by clinical examination, 34 (81%) using AES, and 37 (88%) using MRI (Fig 29). There were 16 horseshoe extensions in this group, 7 (44%) of which were correctly classified by clinical examination, 9 (56%) using AES, and 15 (94%) using MRI.

Clinical Assessment

Fifty-four patients were assessed as outpatients by the 8 consultants and 50 by the 15 senior trainees. There was no significant difference in the distribution of primary or recurrent fistulas between consultants and trainees (11 versus 17 and 43 versus 33 respectively; $p = 0.128$). There was no significant difference between consultants and trainees with respect to accurate digital classification of the primary track (36 of 58 versus 30 of 50; $p=0.84$), internal opening (39 of 53 versus 38 of 46; $p=0.33$), abscess (6 of 25 versus 10 of 23; $p=0.22$) or horseshoe extension (4 of 7 versus 3 of 9; $p=0.61$) when compared to the reference standard.

Agreement-between the modality used and the Reference Standard

Agreement between the modality investigated and the reference standard for classification of the primary track is shown in Table 6 (page 126). Kappa values (95% confidence intervals) for digital assessment, AES, and MRI were 0.38 (0.25-0.5), 0.68 (0.55-0.81), and 0.84 (0.71-0.97), indicating 'fair', 'good', and 'very good' agreement respectively (Landis & Koch, 1977)

Agreement between the modality investigated and the reference standard for classification of both abscesses and horseshoes is shown in Table 7 (page 127). Kappa values (95% confidence intervals) for digital assessment, AES, and MRI were 0.29 (0.2-0.38), 0.64 (0.54-0.74), and 0.88 (0.78-0.98), indicating 'fair', 'good', and 'very good' agreement respectively (Landis & Koch, 1977).

Discussion

A multi-modality study of patients with Crohn's fistula-in-ano found that surgical EUA alone was an inadequate reference standard and suggested it should be combined the results of pre-operative imaging for fistula classification to be accurate (Schwartz et al., 2001). Because of this, we used EUA guided by MRI to try and ensure our reference standard was as accurate as possible, although this meant the reference standard was not truly independent of MRI. However, such modification of the reference standard by one of the modalities under investigation is now a commonly employed procedure where the unmodified reference standard is known to be significantly flawed (Pickhardt *et al* 2003). Indeed, our hospital ethical committee decreed that there was overwhelming evidence that the MRI results had to be available in the operating room if MRI had been performed (Lunniss et al., 1992; Lunniss et al., 1994; Hussain et al., 1996; Spencer et al., 1998; Orsoni et al., 1999; Beets-Tan et al., 2001; Buchanan et al., 2002) and decreed that non-disclosure was unethical. In any event, the pre-operative MR classification had already been established by the radiologist and could not change as a consequence of findings at EUA. Importantly, intra-operative disclosure of MRI findings allowed us to control

for cases where infection might have otherwise been missed by the surgeon, resulting in a false-negative result for MRI.

Clinical follow-up was used to try and ensure the reference standard was as robust as possible because there were instances where the operating surgeon disagreed with MRI. For example, the surgeon occasionally diagnosed a sinus because they could not locate the internal opening that had been seen on MRI. Also, there were instances where the radiologist suggested an abscess that could not be subsequently palpated, and the operating surgeon was unwilling to 'blindly' incise to search for it (see chapter 3). The true fistula classification in such cases can only be resolved by the clinical course following surgery because patients in whom infection has been overlooked will inevitably relapse (ASCRS, 1996a; Soew-Choen & Nicholls, 1992). The outcome-derived reference standard was thus as close as possible to the 'true' fistula classification in each patient and afforded the best means with which to judge the accuracy of the preoperative investigations employed. Most importantly, we wanted to define the relative position of AES, which was why this test was not used to influence the outcome-derived reference standard.

The primary aim of this study was to define the relative accuracy of AES in experienced hands, using a modern 10 MHz transducer. Further, investigators experienced in both AES and MRI were used to eliminate technique bias. The *a priori* hypothesis was that digital examination would fare worst and MRI best, with AES intermediate. This hypothesis was proved correct, with MRI the most accurate modality in all comparisons made. However, although AES was inferior to MRI, it was always superior to clinical examination. Indeed, agreement for AES was

generally 'good', in the category immediately adjacent to MRI ('very good'). Clinical examination tended to be 'fair', which is separated from 'good' by an intermediate category, 'moderate' (Landis & Koch, 1977) AES is therefore likely to be a worthwhile test when MRI or expertise is unavailable. For example, AES correctly classified 81% of all primary tracks in this study and the confidence intervals for AES and MRI overlapped. AES was also especially good at correctly predicting the internal opening in 91% - a figure approaching the 97% achieved by MRI. Identification of the internal opening is a major surgical aim since failure to locate it is highly predictive of recurrence (ASCRS, 1996b)(chapter 3)). AES is well suited to answering this question both rapidly and inexpensively.

AES identified fewer extensions than MRI, probably due to field-of-view limitations. Nevertheless, when considering abscess and horseshoe extensions together, AES still correctly identified the majority, in contrast to clinical examination. However, MRI is undoubtedly the best preoperative modality to detect secondary tracks. Failure to identify and treat these is a common cause of relapse, which explains their prevalence in patients with recurrent disease (Seow-Choen & Nicholls, 1992; ASCRS, 1996a. chapter 3). Seventy-six of the study population had recurrent disease, reflecting the tertiary referral nature of this unit, and it should be borne in mind that this case-mix presents significant difficulties for any imaging modality. Because of this, it was hypothesized that any incremental benefit attributable to MRI over AES might be minimized in patients with primary disease since extensions are less common and infection more likely to be confined to the sphincter complex, thus overcoming field-of-view problems. However, of the 6 abscesses in the 28 patients with primary

disease, AES detected only 2, actually faring worse than clinical examination in this subgroup analysis (the only occasion on which it did so).

It is not clear to what degree these results for AES were influenced by improved transducer technology since this has occurred simultaneously with improved understanding of sonographic anal anatomy as a consequence of endoanal MRI (Hussain et al., 1998; deSouza et al., 1998, Williams et al., 2002). However, endoanal MR receiver coils were not employed because their limited field-of-view makes them less well suited to detection of remote infection (deSouza et al., 1998; Halligan & Bartram, 1998). However, there is no doubt that the shorter focal length provided by a 10MHz transducer provides better spatial resolution than older 7MHz models, both within and adjacent to the anal sphincters (Frudinger et al., 2002).

The present study confirms the relative inaccuracy of outpatient fistula assessment when compared to imaging. It also suggests that digital assessment may not improve with experience because there was no difference between consultants and trainees. However, it should be borne in mind that the trainees were in their last year of subspecialist training and, as for imaging, the high proportion of recurrent cases meant the group was particularly difficult to assess.

Where MRI and expertise are available, these results suggest that the best option for pre-operative assessment would be to progress straight to MRI. Although MRI incorrectly classified 10% of primary tracks when compared to the reference standard, this was predominantly due to minor differences in track description that made little real difference to treatment. For example, there were several instances where the track

crossed the very distal fibres of the subcutaneous EAS, technically a transsphincteric fistula, but often described as intersphincteric on MRI.

This study does have some limitations. It has been suggested that hydrogen peroxide might improve AES (Poen et al., 1998), and this approach is further investigated in Chapter 6. The sonologists had differing levels of experience with AES although all were trained and reporting the examination independently at the time of this study. The difficulties of defining a true reference standard for fistula-in-ano have been discussed above. AES was not used to influence the outcome derived reference standard, which could potentially represent a source of bias, though using clinical outcome as the final arbiter minimized potential biases.

In summary, MRI is the most accurate preoperative technique for classification of fistula-in-ano, and best evaluates the primary track and any extensions. While MRI is generally the preferred technique, AES is demonstrably superior to digital examination and is particularly adept at detecting the internal opening. AES may be used where MRI is unavailable or interpretation expertise is lacking.

Chapter 6:

The value of hydrogen peroxide enhancement of three dimensional endoanal ultrasound in fistula-in-ano

Introduction

While some have suggested AES and MRI are comparable in the assessment of fistula-in-ano (Schwartz et al (2001), the study presented in chapter 5 highlights deficiencies AES has in localising extensions. Several studies authors report improved diagnostic efficacy with contrast enhancement using hydrogen peroxide (Poen et al., 1998; Ratto et al., 2000; Sudol-Szopinska Jakubowski, & Szczepkowski 2002; Kruskal, Kane, & Morrin, 2001), particularly in demonstrating extensions (Ratto et al., 2000).

However, there is an inherent bias in these studies due to a fundamental problem with ultrasound, namely that as recorded images provide insufficient information for diagnosis, examinations have to be interpreted in “real-time” as they are being performed. Contrast enhanced examinations usually have to be performed immediately after the initial ultrasound examination, so that the examiner is therefore always aware of the diagnosis from the initial unenhanced examination. This restriction does not apply to 3D studies, as a complete dataset of the examination is obtained. This may be reviewed in real-time using the cine-loop mode, which simulates actually performing the examination and provides sufficient detail for diagnosis. It is therefore possible for observers to review the enhanced and unenhanced examinations separately, blinded to both the clinical details and the findings on the other study.

Another advantage of 3D examinations is multiplanar reformatting. This means that imaging is not limited to the axial plane in which the images were obtained, and it is possible to cut across any part of the dataset in any coronal, sagittal, or oblique plane. This has been shown to be of diagnostic value when assessing anal canal injury (Gold et al., 1999), but has not been applied to fistula-in-ano.

The aim of this prospective study was to compare the accuracy of 3D-AES and hydrogen peroxide enhanced 3D-AES (HPE 3D-AES) in the classification of recurrent or complex fistula-in-ano, a patient population likely to be rich in extensions. Three-dimensional examinations were used specifically to allow a blinded comparison, and the study was not designed to compare 3D to standard axial imaging.

Methods

Patients

Twenty-three consecutive patients (18 men; median age = 48 years, range 17 to 66) presenting with suspected fistula-in-ano were recruited prospectively. Four patients did not undergo HPE 3D-AES as no external opening could be cannulated, leaving a study population of 19 patients (15 men) who had undergone a median of 3 fistula operations (range 0-19) prior to referral. Four of these had Crohn's disease.

Procedures

All patients underwent preoperative 3D-AES in the lithotomy position, using a B-K Medical 2100 ultrasound system (Herlev, Denmark) an 1850 rotating endoprobe and 10-MHz transducer (type 6004) as detailed in chapter 5. The assembled probe was inserted high enough to visualize the supralelevator space, orientated with anterior uppermost, and then attached to the motor driven puller (Figure 31, page 142), which is an integral part of the 3D software system. Data acquisition during mechanical withdrawal of the probe over a maximum of 6cm takes approximately one minute. The data set was then

saved. Reformatting is rapid and the examination was checked before proceeding to HPE 3D-EAUS. A median of 2.5 ml (range 1-5) of 1.5% hydrogen peroxide was injected via an 4 Fr feeding tube catheter (Vygon, Ecouen, France) inserted into the external fistulous opening (Figure 32, page 142). The pull through was repeated after about 20secs to allow time for bubble release. There was no untoward event following hydrogen peroxide instillation, and all the scans were considered technically adequate.

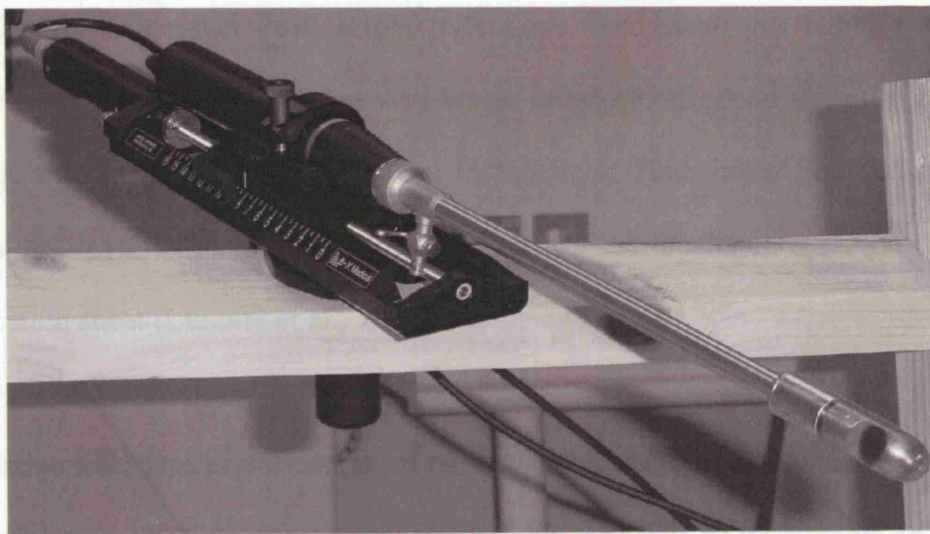


Figure 31: B and K Motor driven puller, holding 10MHz endoprobe

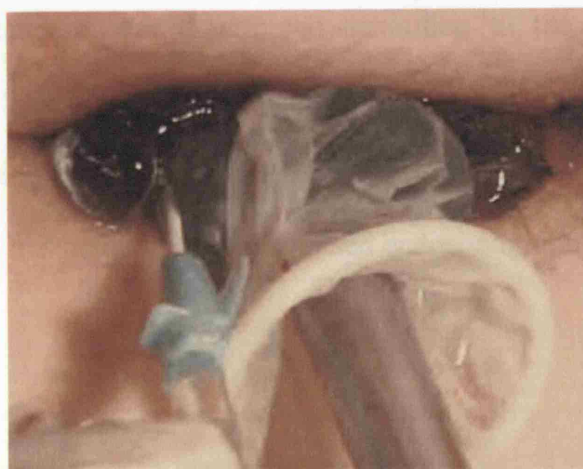


Figure 32: Hydrogen peroxide enhancement of AES.

Cannula inserted into external opening during endosonography

Unenhanced and enhanced examinations were reviewed in a random order by two experienced observers (CIB and GNB) without knowledge of the patient details so as to be blinded to both the clinical findings and abnormalities on any other examination. A consensus classification of the fistula anatomy using Parks classification (Parks, Gordon & Hardcastle, 1976) was derived from both axial and multiplanar image reconstructions. Fistulas were identified on pre-enhancement scans as low reflective tracks that might contain focal bright reflections from small gas bubbles, and after hydrogen peroxide installation as a very bright interface reflection from the gas within the track with acoustic shadowing deep to the track. Examiners recorded their scan findings and level of diagnostic confidence on a visual analogue scale on the fistula classification sheet (Lunniss et al., 1994).

Preoperative MRI was performed in all patients using the body or surface-coil protocol described in chapter 3. Surgery was performed by specialist coloproctologists, who had reported MRI findings available in theatre, but were not given details of the 3D-EAUS findings. The operative findings were documented on a fistula sheet, and the outcome derived reference standard was determined according to the methodology already described in chapter 5. Where internal openings, fistula tracks and extensions had been correctly detected using pre-operative HPE 3D-AES, the two observers retrospectively assessed whether gas had actually been visualised endosonographically.

Statistical analysis

Internal openings were considered correctly identified when described both within the correct quadrant (within two hours on clock face) and level (anal or rectal). The

accuracy of preoperative 3D-AES and HPE 3D-AES for detecting fistulas and classifying internal openings, primary and secondary (horseshoe, abscess) tracks was compared to the reference standard. Categorical frequencies were analysed using Fishers exact test. Level of confidence of 3D-AES and HPE 3D-AES (visual analogue scale) was compared using the Mann-Whitney U test statistic. Analysis was performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, Cambridge, UK). Statistical significance was assigned at the 5% level.

Results

All 19 patients had perianal sepsis, and two with trans-sphincteric fistulas had additional primary tracks (1 extra-sphincteric, 1 superficial), so that there were 21 primary tracks and internal openings in 19 patients (1 superficial, 1 intersphincteric, 18 trans-sphincteric and 1 extra-sphincteric). Patients were followed-up for a median of 13 months (range 4-22). In the 4 patients where follow-up was 10 months or less, there was concordance between MRI and Surgery.

Both 3D-AES and HPE 3D-AES detected only one internal opening in both the cases where two were present. HPE 3D-AES also missed an internal opening associated with a trans-sphincteric track, erroneously classifying this as a sinus. There was no significant difference in the accuracy of 3D-AES and HPE 3D-AES in internal opening evaluation (19/21 (90%) vs. 18/21 (86%); $p=1$, see table 8).

Both techniques identified the fistula track in the correct radial position in 19/21 (90%) cases. HPE 3D-AES missed an additional superficial primary track associated with a trans-sphincteric fistula, which was clearly shown on the non-enhanced 3D-AES. Both

techniques missed the extra-sphincteric fistula. With regards to fistula localisation in the correct anatomical plane, HPE 3D-AES misclassified 4 trans-sphincteric tracks as intersphincteric, whereas 3D-AES misclassified one as intersphincteric and one as superficial. Overall there was no significant difference between 3D-AES and HPE 3D-AES in primary track anatomical classification (17/21 (81%) vs. 15/21 (71%); $p=0.072$, see table 8).

Table 8: The accuracy of 3D-AES compared to HPE 3D-AES for correct fistula classification in 19 patients

| Classification | | 3D-AES | HPE 3D- AES | Reference |
|-------------------------|-------------------|-----------|-------------|-----------|
| Internal opening | Anal | 19 | 18 | 20 |
| | Rectal | 0 | 0 | 1 |
| | Total | 19 | 18 | 21 |
| Primary track | Sinus | 0 | 0 | 0 |
| | Superficial | 1 | 0 | 1 |
| | Intersphincteric | 0 | 1 | 1 |
| | Trans-sphincteric | 16 | 14 | 18 |
| | Supra-sphincteric | 0 | 0 | 0 |
| | Extra-sphincteric | 0 | 0 | 1 |
| | Total | 17 | 15 | 21 |
| Secondary track | Superficial | 0 | 1 | 3 |
| | Intersphincteric | 2 | 1 | 2 |
| | Ischiorectal | 10 | 9 | 12 |
| | Supralevator | 1 | 1 | 2 |
| | Total | 13 | 12 | 19 |

NB: 2 patients were found to have 2 primary tracks.

Fourteen patients had 19 secondary tracks (abscesses and horseshoe extensions). 3D-AES missed all three superficial extensions and HPE 3D-AES missed 2, and 1 intersphincteric extension. Two and 3 ischiorectal extensions respectively were not visualised, and both missed 1 supra-levator extension. Overall, there was no difference in the accuracy of 3D-AES and HPE 3D-AES in extension detection (13/19 (68%) vs. 12/19 (63%); $p=1.0$).

On hydrogen peroxide enhanced studies gas was present in 8/18 (44%) of the internal openings detected on AES. The fistula tracks were more obvious in 6/19 (32%) and the secondary tracks in only 6/13 (46%) of those detected.

Confidence of assessments

There was no significant difference in the level of diagnostic confidence displayed by either observer with or without contrast enhancement (median confidence 7 (range 3-9) vs. 7 (range 4-9) median; $p=0.83$).

Discussion

Hydrogen peroxide is commonly used at surgery to localise the internal opening (Gunawardhana & Deen, 2001), and in view of this it is surprising that enhancement did not improve endosonographic detection. Un-enhanced 3D-AES was 95% correct in localising internal openings in the anal canal. This may be due to better understanding of the endosonographic criteria for the definition of the internal opening (Cho, 1999), as well as improvements in image quality. Furthermore, fistulas may exit the anal canal

obliquely from the internal opening (this is further studied in chapter 8). The multi-planar properties of 3D-AES enabled the plane of the track to be visualised, which helped localise the internal opening (Figure 33, page 147). Gas tracked down into the internal opening in only 44% (Figure 34, page 148), so that if gas enhancement of the internal opening were relied upon for diagnosis, less than half would have been diagnosed. Inadequate technique could be an explanation, but other studies have shown 48% (Poen et al., 198) and 54% (Ratto et al., 2000) internal opening localisation using hydrogen peroxide, which would be in keeping with our findings if the diagnosis was based solely on the presence of gas.

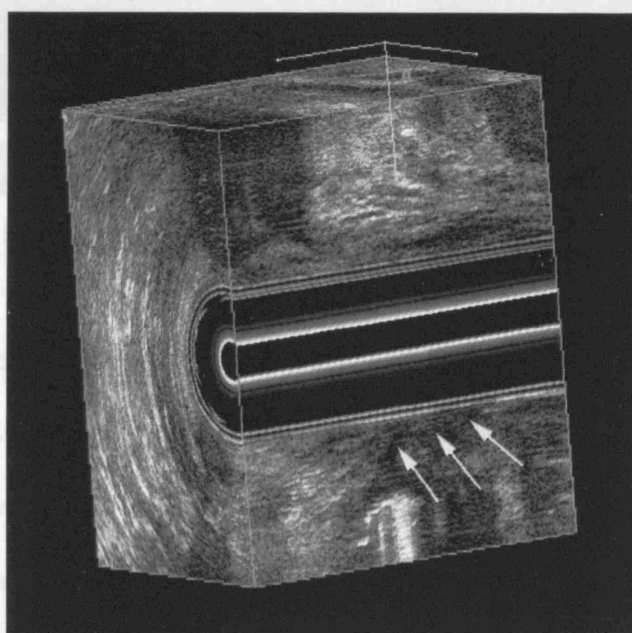


Figure 33: Sagittal 3D-AES

Sagittal image in the mid canal plane showing an obliquely angled internal opening (arrows) from a trans-sphincteric track.

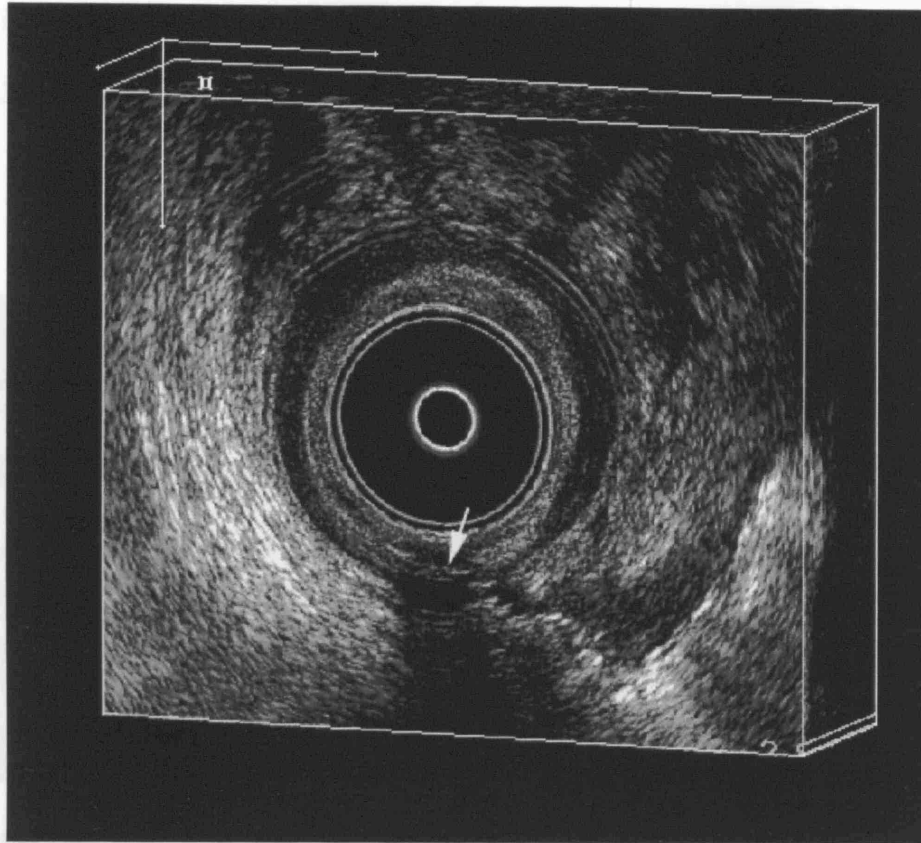


Figure 34: Axial image post enhancement showing gas within a trans-sphincteric track.

This extends into the internal opening (arrow).

Surgical localisation of fistula-in-ano using hydrogen peroxide is reliant on direct visualisation of bubbles emanating through the internal opening. Both techniques involve digital pressure to prevent gas bubbling back through the external opening. However, any exudate or debris impeding track patency is likely to be more easily expelled by deeper cannula placement and more forceful hydrogen peroxide instillation at surgery than in the conscious patient undergoing endosonography. This may also explain why only 32% of fistulas and 46% of the secondary tracks filled completely with gas, a finding that counters claims that demonstrating extensions is one of the advantages of contrast enhancement (Ratto et al., 2000). Another explanation is that gas will pass preferentially along the track of least resistance, and may therefore discharge

via the internal opening from the primary track without filling a secondary extension (Figure 35a&b).

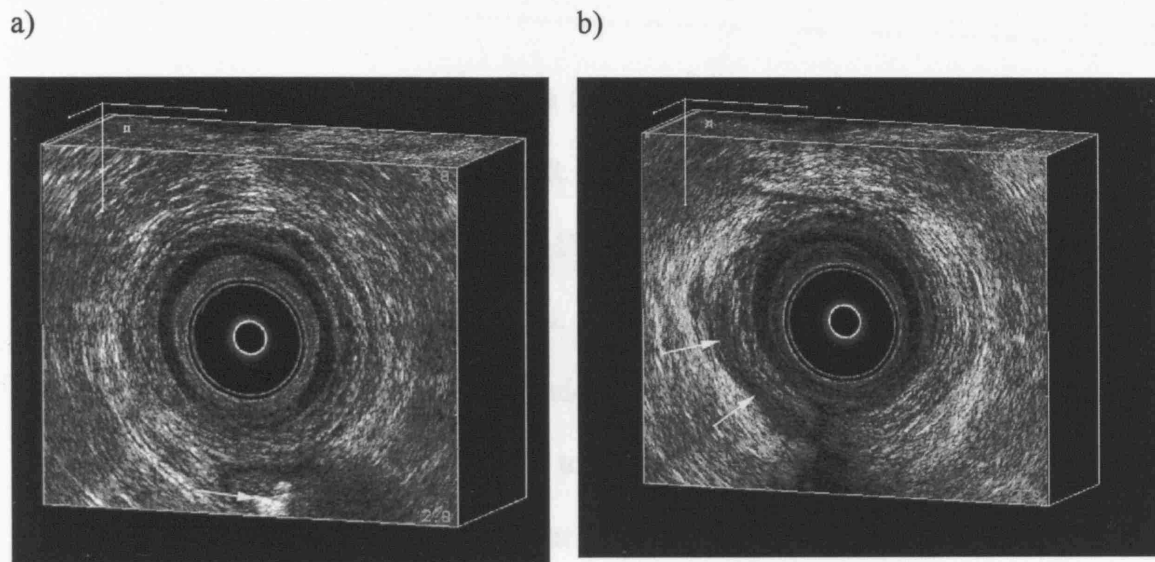


Figure 35: Gas failing to enter extension:

Axial images with gas (arrow) in a primary trans-sphincteric track at 6 o'clock (a), which failed to extend into the internal opening and secondary track (arrows) at a higher level (b).

The present study employed a reference standard based upon surgery guided by MRI, which was modified where necessary by findings on follow-up as described in chapter 5. As MRI is more accurate than surgical findings, particularly in assessing extensions (Spencer et al., 1998), we believe this reference standard accurate for the true fistula classification. Furthermore, in those where follow-up was short, MRI and surgical findings were concordant.

All the patients in this study had recurrent or complex fistula. Previous surgery can complicate endosonographic diagnosis as, unlike MRI, there is no clear difference between scar and inflammatory tissues. However, in practice this was not as much of a problem as it has been considered previously (Choen et al., 1991). Recurrent fistula

usually have a more complicated track system, and this may contribute to poorer diagnostic efficacy in comparison to other studies where most of the fistulae were primary (Poen et al., 1998)

Hydrogen peroxide is generally very safe to use. Gas embolism has been induced after irrigation of an abscess cavity (Schwab & Dilworth, 1999) or following large volumes used during surgery (Gunawardhana & Deen, 2001), particularly when it is instilled under high pressure (Garcia-Velasco et al. 1997). The small volumes and low pressures used for contrast enhancement during endosonography are most unlikely to cause any problem, and none has been reported to date. A disadvantage that is inherent to ultrasound is the very strong reflection that occurs at a gas/tissue interface, which blanks out any detail deep to this interface. The large bubbles produced by hydrogen peroxide induce acoustic shadowing deep to the track so that all information deep to the inner surface of the track is lost (Figure 36a&b, page 151).

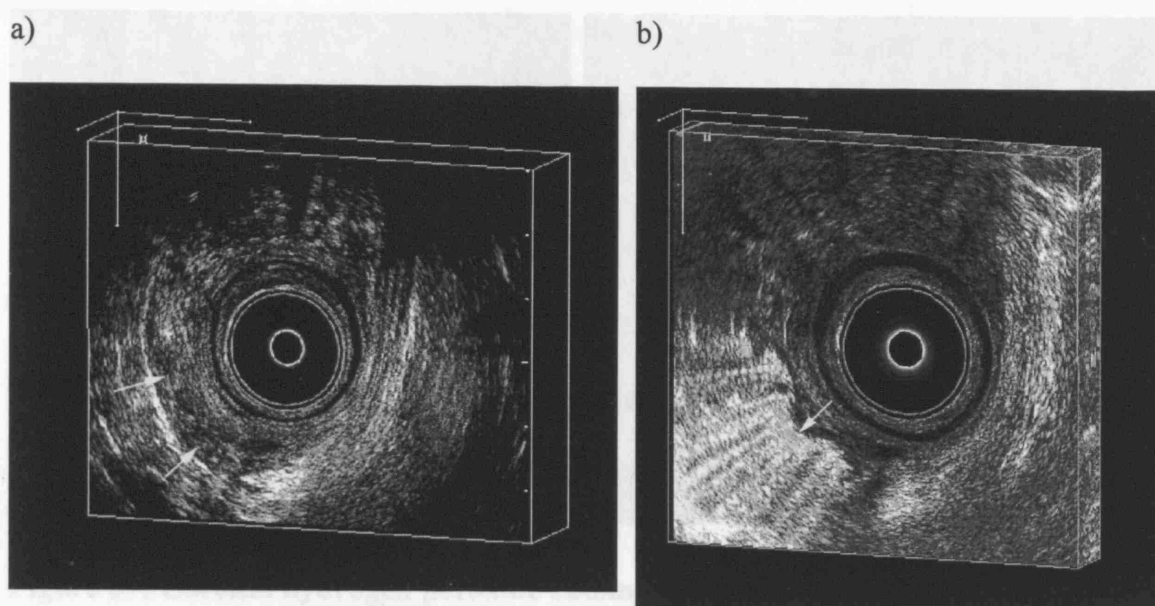


Figure 36: Axial EAUS images pre (a) and post (b) hydrogen peroxide enhancement.

The secondary ischio-anal extension from the primary trans-sphincteric track at 7 is clearly visible (arrows) on both pre and post enhancement. Note the strong echoes produced from the gas interface (arrow) (b) and complete acoustic shadowing of any deeper structure this produces.

Three-dimensional studies were used mainly to enable blinded comparisons, and it was not part of the experimental design to investigate the value of multiplanar imaging in fistula. Diagnosis was undertaken mainly from cine-looping through the dataset in the axial plane where image quality was optimum. Reconstructed images in other planes were not of similar quality, as the pixel size was not isotropic and on some examinations artefact was induced as the probe was pulled back through the anal canal. Nevertheless multiplanar imaging was found to be very helpful in tracing the pathway of a track (Fig 37a&b, page 152), and internal openings (Figure 32, page 142), so that diagnostic confidence was improved with multiplanar reformatting.

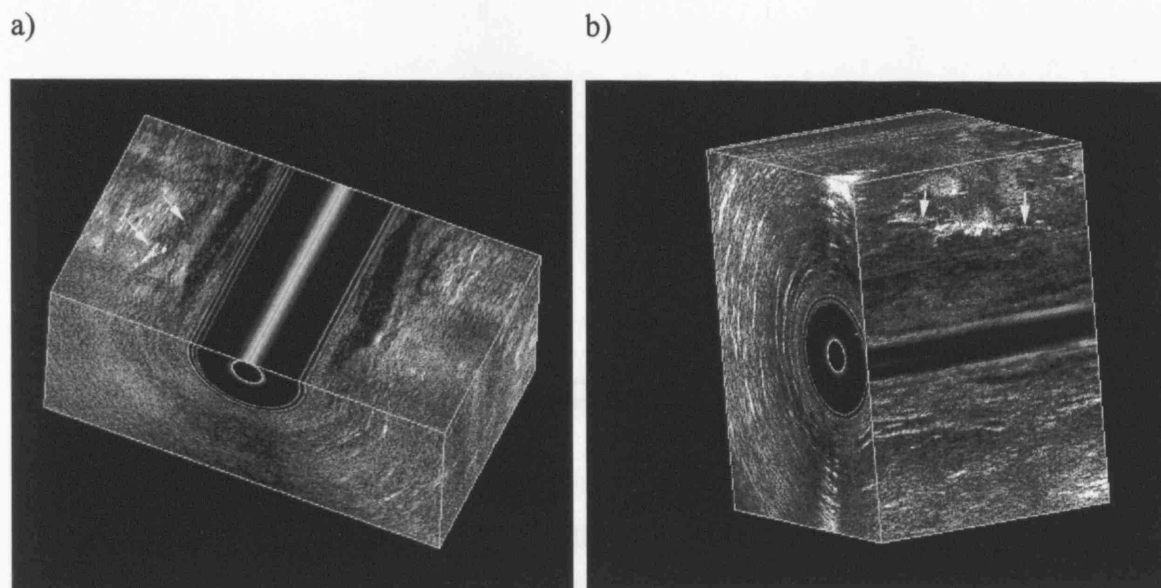


Figure 37: Coronal hydrogen peroxide enhanced 3D-AES

Coronal image (a) with gas in a trans-sphincteric track (arrows) and a sagittal reconstruction (b) showing the path of the track (arrows)

In summary, in recurrent or complex fistula-in-ano, 3D-EAUS accurately identifies primary tracks and internal openings, though does not clearly define extensions. Hydrogen peroxide has some benefit in making tracks more conspicuous and may be useful in difficult cases.

Chapter 7:

Magnetic resonance imaging of fistula-in-ano:

Inter- and Intra- observer agreement

and effects of directed education.

Introduction

Magnetic resonance imaging may become routine for assessment of complex or recurrent fistula (Beets-Tan et al., 2001: chapter 3). However, most MRI studies have originated from specialist centres where radiologists are familiar with anorectal anatomy and the different types of fistula. Although good reproducibility for MRI interpretation has been demonstrated between experienced observers (Beets-Tan et al., 2001) poor reproducibility by inexperienced radiologists may negate the potential value of imaging in this condition (Schofield et al., 1997). The level of agreement between experienced and inexperienced observers has not been described. This prospective study assessed whether there was a significant difference in interpretation between an expert and a novice observer, and inter- and intra-observer agreement after a period of directed education in MRI interpretation.

Methods

One hundred consecutive patients (71 male; median age 42 years, range 17 to 65 years) with suspected fistula-in-ano were recruited as part of an ongoing prospective trial assessing the value of preoperative MRI (see chapters 3 and 4). Each patient underwent MRI according to the protocol in chapter 3, and subsequently underwent EUA with the benefit of the MRI as described in chapter 3. Patients were followed up in outpatients for a median duration of 18 months, range 10 to 46 months and an outcome derived reference standard fistula classification achieved as described in chapter 5.

The 100 cases were then divided into two groups of 50 by the principal investigator (GB), matched for demographic features and fistula complexity (Table 1, page 64). The first group of 50 patients was assessed independently by two observers blinded to MRI reports, surgical findings, and clinical outcome. The expert observer (SH) was a consultant gastrointestinal radiologist with extensive experience of reporting MRI studies for fistula-in-ano (see chapter 3). The novice observer was a fourth-year radiology trainee with a subspecialty interest in gastrointestinal imaging, and who had just commenced a fellowship in this. The novice (ST) had no prior training in reporting MRI for fistula-in-ano and had not experienced any specific training in abdomino-pelvic MRI in general. The novice had prepared for this study by reading peer-reviewed literature relevant to the topic.

The two observers recorded their findings on a fistula classification sheet. Primary tracks were classified according to Park's method (Parks, Gordon & Hardcastle, 1976). If there was no internal opening then the track was classified as a sinus. If multiple fistulas were present, these were recorded together on the same sheet. (Markantonis, 1974). The radial site of the internal opening was defined in relation to a clockface as per usual surgical clockface (6 o'clock posterior) and its level was recorded as either rectal or anal. Any associated secondary extensions (abscesses and/or horseshoe extensions) were defined by their anatomical quadrant and location; ischiorectal, intersphincteric, or supralelevator (Parks, Gordon & Hardcastle, 1976).

The principal investigator then determined the level of agreement between the observers' assessments and the outcome derived reference standard. Any categorical discrepancy relating to the primary fistula track classification was considered a

disagreement. The radial site of the internal opening was considered correct if recorded to within one-quadrant on the clock-face and its level judged correct if the correct category for the enteric opening had been indicated (rectal or anal). Disagreement for the presence or absence of any extension was noted and further disagreement noted if the anatomical site or quadrant had been recorded incorrectly by the observer.

The principal investigator then undertook a detailed review with each observer independently. This entailed comparing the completed observer classification sheet and outcome derived reference standard on a case-by-case basis. The precise nature of any disagreement between the two assessments was flagged by the principal investigator and verbally discussed with the observer during re-review of the MRI hard-copy films on a viewing box. All studies were reviewed, including those where the observer's assessment was judged correct, and the whole process took approximately three-hours for each observer. Each observer was therefore educated on a case-by-case basis.

Each observer then independently reported the second group of 50 MRI scans in an identical fashion to the first, submitting findings to the principal investigator when assessment was complete. In order to assess intra-observer agreement, each observer performed a further assessment of the second group of cases, which was undertaken blinded to the previous assessment and which was performed at least a month after, with the film order shuffled, in an attempt to eliminate recall bias. Comparison with the outcome-derived reference standard was again performed and agreement determined.

Statistical Analysis

Any significant differences between the diagnostic accuracy of each observer for the two groups of 50 cases were determined by comparing their assessments with the outcome derived reference standard. Primary tracks and abscess/horseshoe extensions were considered correctly identified when described in the correct anatomical location according to the reference standard. Internal openings were considered correctly identified when described within the same quadrant (defined as within 2 hours on the clockface), and at the same level (anal or rectal) as the reference standard. Differences in categorical frequencies between the two observers were compared using Fishers exact test. Strength of agreement between the two observers for the second group of 50 studies was determined using the Kappa test statistic (Landis & Koch, 1977). Analysis was performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, Cambridge, UK). Statistical significance was assigned to a probability level of less than 0.05 and levels of agreement were defined according to Landis and Koch (1977).

Results

Of the 100 patients, 4 (4%) patients had no sepsis, 6 had sinuses (6%) and 90 (90%) had 96 fistulas (Table 9).

Correct classification

The experienced observer correctly classified significantly more fistula tracks than the novice (85% versus 63%, $p = 0.024$; Table 10, page 161) (Figure 38, page 168) when the first 50 studies were assessed but there was no significant difference between them for the second 50, following the period of directed education (85% versus 72% and 83%

versus 76% for each of the two second reads respectively, $p=0.16$ and 0.47 respectively; Table 10, page 161) (Figure 39, page 168). There was no significant difference between the expert and novice observer for correct identification of abscess or horseshoe extensions, or internal openings when the first and second groups were compared (Table 10, page 161).

Inter-observer agreement

Following the period of directed education, there was 'good' agreement (Kappa 0.71, Table 11, page 162) between the expert and novice for classification of the primary track and also 'good' agreement (Kappa 0.61, Table 12, page 163) for the identification and localisation of extensions (Landis & Koch, 1977)

Table 9: Characteristics of two groups of patients with fistula-in-ano

| | First group | Second group | |
|--------------------------------|--------------------|---------------------|-----------|
| | <i>N=50</i> | <i>N=50</i> | P* |
| Age; median (range) | 39 (22-65) | 44 (17-65) | 0.21 |
| Sex (m:f) | 34:16 | 36:14 | 0.66 |
| Primary / Recurrent | 18:32 | 14:36 | 0.39 |
| Crohns disease | 7 | 3 | 0.31 |
| Draining seton** | 7 | 4 | 0.52 |
| Previous operations | 2 (0-25) | 3 (0-19) | 0.21 |
| Simple: Complex | 18:32 | 19:31 | 1 |
| Fistulas | | | |
| Nil | 1 | 3 | 0.618 |
| Sinus | 4 | 2 | 0.433 |
| Superficial / Intersphincteric | 21 | 17 | 0.419 |
| Trans-sphincteric | 22 | 28 | 0.339 |
| Suprasphincteric | 4 | 1 | 0.201 |
| Extrasphincteric | 0 | 3 | 0.243 |
| Abscess | 23 | 24 | 1 |
| Horseshoe extensions | 8 | 8 | 1 |
| Internal opening | Anal | 46 | 0.242 |
| | Rectal | 3 | |

*Fishers Exact test for categorical data; Mann-Whitney U test for continuous data, N=number. ** A surgical thread placed to provide drainage.

Table 10: Comparison of correct fistula classifications achieved by the expert and novice observer for the first fifty MR imaging examinations and for the second fifty following directed education.

(N, n=number)

Feature correctly classified n (%)

| Feature examined | First 50 | | | | | | Second 50 | | | | | |
|----------------------------|-----------------|---------|--------------|----------------------------|---------|---------|------------------|---------|---------|---------------|-------|----|
| | Expert | | | Novice | | | Expert | | | Novice | | |
| | N (%) | N (%) | P* | N (%) | N (%) | P* | N (%) | N (%) | P* | N (%) | N (%) | P* |
| Primary tracks (n = 52) | 44 (85) | 33 (63) | 0.024 | Primary tracks (n = 54) | 46 (85) | 39 (72) | 0.16 | 45 (83) | 41 (76) | 0.47 | | |
| Abscess (n = 23) | 17 (74) | 14 (61) | 0.530 | Abscess (n = 24) | 18 (75) | 13 (54) | 0.22 | 16 (67) | 14 (58) | 0.77 | | |
| Horseshoes (n = 8) | 7 (88) | 3 (38) | 0.119 | Horseshoes (n = 8) | 5 (63) | 5 (63) | 1.00 | 7 (88) | 5 (63) | 0.57 | | |
| Internal openings (n = 47) | 44 (94) | 44 (94) | 1.000 | Internal openings (n = 49) | 43 (88) | 42 (86) | 1.00 | 44 (90) | 42 (86) | 0.76 | | |

*Fishers exact test

Table 11: Inter-observer agreement between the expert and novice for classification of the primary fistula track following directed education
(Four patients had 2 fistulas).

| | Expert observer | | | | | | Total Kappa |
|---------------------------------|-----------------|-----------------------|---------------------------------|-------------------|-------------------|-------------------|-------------|
| | No sepsis | Sinus or subcutaneous | Superficial or intersphincteric | Trans-sphincteric | Supra-sphincteric | Extra-sphincteric | |
| Novice observer | | | | | | | |
| No sepsis | 4 | 0 | 1 | 0 | 0 | 0 | 5 |
| Sinus or subcutaneous | 0 | 2 | 3 | 0 | 0 | 0 | 5 |
| Superficial or intersphincteric | 1 | 0 | 11 | 0 | 0 | 0 | 12 |
| Trans-sphincteric | 1 | 0 | 3 | 26 | 0 | 1 | 31 |
| Suprasphincteric | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Extrasphincteric | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | 6 | 2 | 18 | 26 | 0 | 2 | 54 0.71 |

Table 12: Inter-observer agreement between the expert and novice for classification of the identification and localisation of extensions following directed education

| Novice observer | Expert observer | | | | | | | |
|----------------------------|-----------------|-----------|-----------|-----------|------------------|-----------|-----------|--------------------------|
| | Superficial | | | | Intersphincteric | | | |
| | Nil | extension | extension | extension | horseshoe | extension | horseshoe | Suprlevator horseshoe |
| Nil | 24 | 3 | 1 | 1 | 0 | 0 | 0 | 29 |
| Superficial extension | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 5 |
| Intersphincteric extension | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| Intersphincteric horseshoe | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 4 |
| Ischiorectal extension | 1 | 0 | 0 | 9 | 0 | 0 | 0 | 10 |
| Ischiorectal horseshoe | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 3 |
| Suprlevator extension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Suprlevator horseshoe | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | 30 | 5 | 1 | 11 | 3 | 3 | 1 | 57 |
| | | | | | | | | 0.61 |

Table 13: Intra-observer agreement for expert and novice observers for classification of the primary fistula track following directed education.

| | Expert observer first read | | | | | Total Kappa |
|------------------------------------|----------------------------|-----------------------|---------------------------------|-------------------|-------------------|-------------------|
| | No sepsis | Sinus or subcutaneous | Superficial or intersphincteric | Trans-sphincteric | Supra-sphincteric | Extra-sphincteric |
| Expert observer second read | | | | | | |
| No sepsis | 6 | 0 | 0 | 0 | 0 | 6 |
| Sinus or subcutaneous | 0 | 1 | 0 | 1 | 0 | 2 |
| Superficial or intersphincteric | 0 | 1 | 18 | 0 | 0 | 19 |
| Trans-sphincteric | 0 | 0 | 0 | 24 | 0 | 24 |
| Suprasphincteric | 0 | 0 | 0 | 1 | 0 | 1 |
| Extrasphincteric | 0 | 0 | 0 | 0 | 2 | 2 |
| Total | 6 | 2 | 18 | 26 | 0 | 54 |
| | | | | | | 0.92 |

| | | Novice observer first read | | | | | Total Kappa |
|------------------------------------|--|----------------------------|-----------------------|---------------------------------|-------------------|-------------------|-------------------|
| | | No sepsis | Sinus or subcutaneous | Superficial or intersphincteric | Trans-sphincteric | Supra-sphincteric | Extra-sphincteric |
| Novice observer second read | | | | | | | |
| No sepsis | | 4 | 0 | 0 | 0 | 0 | 4 |
| Sinus or subcutaneous | | 0 | 5 | 1 | 0 | 0 | 6 |
| Superficial or intersphincteric | | 0 | 0 | 11 | 2 | 0 | 13 |
| Trans-sphincteric | | 1 | 0 | 0 | 29 | 0 | 30 |
| Suprasphincteric | | 0 | 0 | 0 | 0 | 0 | 0 |
| Extrasphincteric | | 0 | 0 | 0 | 0 | 0 | 1 |
| Total | | 5 | 5 | 12 | 31 | 0 | 54 |
| | | | | | | | 0.88 |

Table 14: Intra-observer agreement for expert and novice observers for identification and localisation of extensions following directed education.

| | | Expert observer first read | | | | | | | | | | Total | Kappa |
|-----------------------------|----|----------------------------|-----------|------------------|-----------|--------------|-----------|-------------|-----------|-------------|----|-------|-------|
| | | Superficial | | Intersphincteric | | Ischiorectal | | Suprlevator | | Suprlevator | | | |
| Nil | | extension | extension | horseshoe | extension | horseshoe | extension | horseshoe | extension | horseshoe | | | |
| Expert observer second Read | | | | | | | | | | | | | |
| Nil | 23 | 3 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 29 | | |
| Superficial extension | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | | |
| Intersphincteric extension | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | | |
| Intersphincteric horseshoe | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 4 | | |
| Ischiorectal extension | 2 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 | 0 | 11 | | |
| Ischiorectal horseshoe | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 | | |
| Suprlevator extension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | | |
| Suprlevator horseshoe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | | |
| Total | 30 | 5 | 1 | 3 | 11 | 3 | 3 | 1 | 3 | 1 | 57 | 0.64 | |

Novice observer first read

| Novice observer second Read | Novice observer first read | | | | | | | | Total Kappa |
|--------------------------------|----------------------------|------------------------------|-----------|------------------|-----------|--------------|-----------|-------------|-------------|
| | Nil | Superficial Intersphincteric | | Intersphincteric | | Ischiorectal | | Suprlevator | |
| | | extension | extension | horseshoe | extension | horseshoe | extension | horseshoe | |
| Nil | 26 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 31 |
| Superficial extension | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Intersphincteric extension | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 4 |
| Intersphincteric horseshoe | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 3 |
| Ischiorectal extension | 1 | 0 | 0 | 1 | 9 | 0 | 0 | 0 | 11 |
| Ischiorectal horseshoe | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 |
| Suprlevator extension | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 |
| Suprlevator horseshoe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | 29 | 4 | 2 | 4 | 11 | 3 | 3 | 1 | 57 |
| | | | | | | | | | 0.74 |

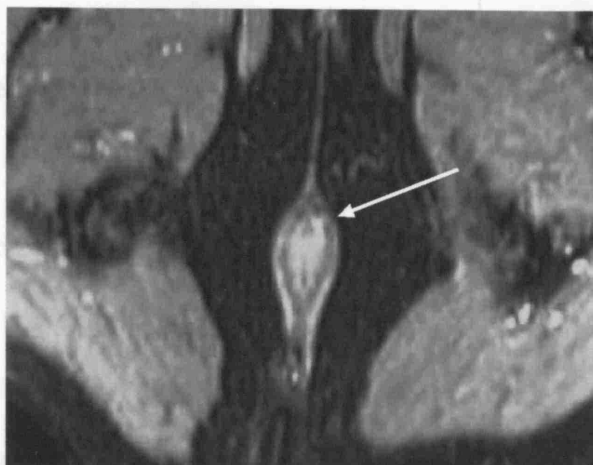


Figure 38: MRI where expert and novice disagree

Axial STIR MR image at mid anal canal level in a 41 year old male, in whom the expert observer correctly identified an intersphincteric fistula-in-ano (arrowed). This was misclassified as trans-sphincteric by the novice prior to directed education.



Figure 39: MRI where expert and novice agree after education

Axial STIR MR image at mid anal canal level in a 36 year old female, in whom both the expert and novice observers correctly identified a trans-sphincteric fistula-in-ano associated with an ischioanal extension (arrowed) following a period of directed education.

Intra-observer agreement

Following the period of directed education, there was ‘very good’ intra-observer agreement for both the expert (Kappa 0.92, Table 13, page 164) and novice (Kappa 0.88, Table 13, page 164) for classification of the primary track (Landis & Koch, 1977). Intra-observer agreement for identification and anatomical localisation of extensions was ‘good’ for both the expert (Kappa 0.64, Table 14, page 166) and the novice (Kappa 0.74, Table 14, page 166) (Landis & Koch, 1977).

Discussion

This study has shown a significant difference in the correct classification of fistula-in-ano with MRI between a single expert and novice observer. This is not surprising as it has long been recognised that experts perform better than generalists on the presumption that their subspecialty experience enhances their ability to interpret new cases based on prior experience, and they understand the clinical context more readily (Halligan, 2002; Robinson, 1997). Supporting this, an MRI study of 27 patients with fistula-in-ano found that only 42% of fistula were correctly classified by a radiologist new to the technique (Schofield et al., 1997). However, the authors were able to demonstrate that correct interpretation rose to 50% by the end of the study, and suggested that a learning curve was responsible (Schofield et al., 1997). Nevertheless, this figure is still well short of those achieved using experienced radiologists (Lunniss et al., 1994; Spencer et al., 1996), chapters 3,4).

Surprisingly, no significant difference between expert and novice observers was found when the identification and anatomical localisation of extensions was considered, even before the period of directed education was undertaken. This implies that the major challenge for radiologists embarking on pre-operative MRI for fistula-in-ano lies with correct classification of the primary track (i.e. into inter-, trans-, supra-, and extra-sphincteric) rather than the identification of extensions. Beets-Tan and co-workers (2001) found good to very good agreement between an experienced radiologist and a radiology resident although it is unclear whether the resident was also experienced in interpretation of fistula MRI. Like the present study, agreement was best for detection of extensions rather than track classification (Beets-Tan et al., 2001). In the present study no significant difference (and 'good' agreement) between expert and novices was demonstrable after directed education, suggesting that the technique may be rapidly mastered given the right training environment (Figure 39, page 168). Both observers were radiologists and, intra-observer agreement was 'very good' for classification of the primary track, suggesting that the technique may be highly reproducible if the same observer is used for any follow-up studies. An outcome-derived reference standard (chapter 5) was employed to ensure that incorrect reference classifications did not confound assessments of observer accuracy.

This study does have some limitations, notably that only one expert and novice was used. Given this, each is effectively acting as a proxy for all experts and novices respectively. While our expert really was so, based on substantial personal experience and previous performance in blinded MRI comparisons (chapters 3-5; (Buchanan et al. 2003b; Halligan & Bartram 1998; Taylor, Halligan, & Bartram 2003)), it could be argued that the novice, because of their declared subspecialty interest in gastrointestinal

radiology, may have been unusually receptive to directed training in this field. Nevertheless, they had not been responsible for reporting MRI examinations for fistula-in-ano prior to the study yet had achieved statistical parity with the expert by the end of it. Anecdotally, experience with other novices suggests that training is generally straightforward and depends most upon a thorough understanding of the disease pathogenesis and the surgical issues (Halligan, 1998), the imaging and interpretation is generally straightforward once these are understood. Adequate performance seems achievable after only a few hours of directed training with an expert as long as the novice understands the pathogenesis and treatment of fistula-in-ano. Whether there is enough expertise presently to provide this training is unknown but increasing surgical awareness of the technique will inevitably increase demand.

In summary, this study suggests that experts perform significantly better than novices for pre-operative classification of fistula-in-ano using MRI, but that novices can achieve acceptable performance following a period of directed education. Following directed education, agreement between experts and novices is 'good' and intra-observer agreement is also acceptable.

Chapter 8:

Potential clinical implications of the direction of the trans-sphincteric fistula track through the sphincter complex

Introduction

Parks' classification of fistula-in-ano indicates trans-sphincteric fistula crossing the anal sphincter complex at right angles to the longitudinal axis of the anal canal (Parks, Gordon & Hardcastle, 1976). Clinical observation suggests that these tracks may pass obliquely, which would increase the longitudinal extent of sphincter divided at fistulotomy relative to the level of the internal opening. There is currently no information on the longitudinal direction of trans-sphincteric fistula through the sphincter. MRI identifies the anal sphincter anatomy clearly (Morren et al., 2001), and classifies anal fistula accurately (Abel et al. 1993; Beets-Tan, et al., 2001; Lunniss, et al., 1992; Venkatesh & Ramanujam 1999). This prospective study used preoperative MRI to determine the angle at which a trans-sphincteric fistulous track passes through the sphincter complex in relation to the long axis of the anal canal.

Methods

Patients

Forty-six consecutive patients (34 men; median age = 44 years, range 17 to 65) presenting with trans-sphincteric fistulas were studied prospectively as part of an ongoing trial assessing the value of preoperative MRI at EUA (chapters 3,4). Four had Crohn's disease. Patients had previously undergone a median of 3 fistula operations (range 0-19).

MR Imaging and assessment

Preoperative body coil MRI was performed a median of 2 days prior to surgery (range same day to 183 days), using the protocol described in chapter 3. Thirty-six of the 46 patients had EUA within one month of their MRI. MRI scans were reported by the supervising radiologist without knowledge of the clinical findings, using a fistula classification sheet, which was made available to the surgeon at subsequent EUA (chapter 3 and 4).

All MR Images were reviewed by one consultant gastrointestinal radiologist (SH), to determine the angle at which the fistula crossed the anal sphincter complex on the coronal image. The most medial point of the internal opening was initially established and marked, and a line was subtended between this point and the point at which the fistula track crossed the outer aspect of the external sphincter. The angle between this line and the long axis of the anal canal was measured to the nearest whole degree.

Examination under Anaesthetic

The EUA was performed by one of seven consultant coloproctologists in 41 patients. Five different year six trainees operated on the remaining five. Probing or hydrogen peroxide instilled via the external opening helped delineate the track and internal opening, though where this was unsuccessful or there was no external opening, core out fistulectomy or a radial circumferential incision was employed to define anatomy and facilitate access. At the end of the operation each surgeon completed a fistula classification sheet similar to the one used for MRI reporting, detailing their findings

regarding the course of the primary track, the site and level of the internal opening and secondary extension.

(Version 1.2, Research Solutions, Cambridge, UK). Statistical significance was assigned to a probability level of less than 0.05.

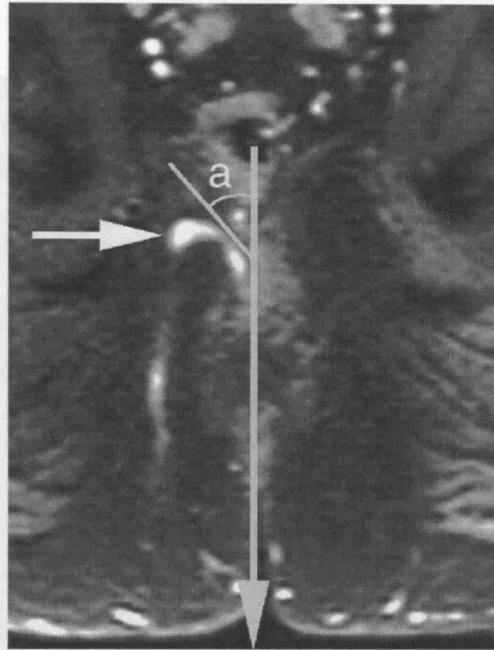


Figure 40: Acute trans-sphincteric fistula

STIR Coronal MRI of a trans-sphincteric fistula (arrowed) passing through the anal sphincter complex at an acute (a) angle from its internal opening.

Statistical analysis

Patients were divided into two groups based on the preoperative MRI findings according to whether the track passed cranially as well as laterally from the internal opening at an acute angle ($< 90^\circ$) (Figure 40, page 175), or either transversely or caudally at an obtuse angle ($90-180^\circ$) (Figure 41, page 176). These findings were compared with the level of the internal opening in relation to the dentate line found at surgery. Categorical frequencies were analysed using Fishers exact test, chi-squared test and chi-squared test for trend. Continuous variables were analysed using the Mann-Whitney U test statistic. Differences in track angulation compared to internal opening

level were analysed using the Kruskal-Wallis test. Analysis was performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, Cambridge, UK). Statistical significance was assigned to a probability level of less than 0.05.

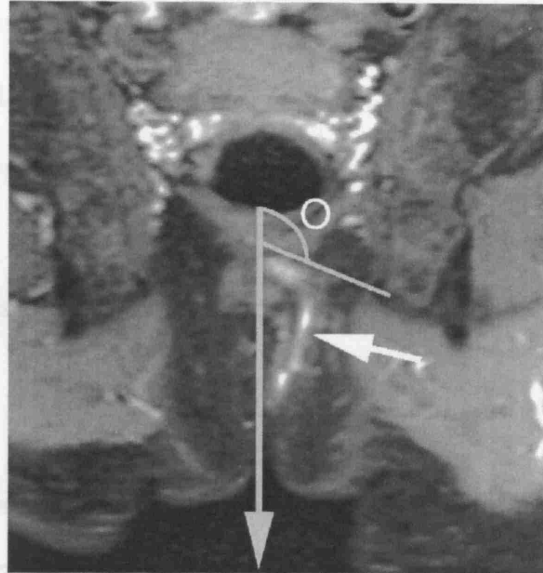


Figure 41: Obtuse trans-sphincteric fistula

STIR Coronal MRI of a trans-sphincteric fistula (arrowed) passing through the anal sphincter complex at an obtuse (o) angle from its internal opening.

Results

Angle of fistula track on MRI

Of the 46 patients, there were 23 in whom the preoperative MRI showed the trans-sphincteric track passing cranially as well as laterally from the internal opening through the sphincter at an acute angle ($< 90^\circ$), while in 23 it passed either transversely or caudally at an obtuse angle ($\geq 90^\circ$). The distribution of track angulation is displayed in Figure 41. Almost one third of the patients had tracks that were acutely angulated at less than 60° .

Demography

There was no relationship between age, sex, number of previous operations or proportion of patients with Crohn's disease or recurrent fistula and the direction of the track (Table 15, page 180).

Fistula characteristics

Primary track

All 46 patients had a trans-sphincteric fistula identified by preoperative MRI and confirmed at EUA. Of 23 patients (Table 16, page 181) with an acute track, 2 additionally had an extra-sphincteric fistula branching off this main track and opening into the rectum, whereas none of the 23 patients with obtuse tracks had an extra-sphincteric fistula. In both of these cases the operating surgeon could not demonstrate the trans-sphincteric track by probing owing to its acute angulation. Furthermore, neither patient had Crohn's or evidence of any active disease in the rectum.

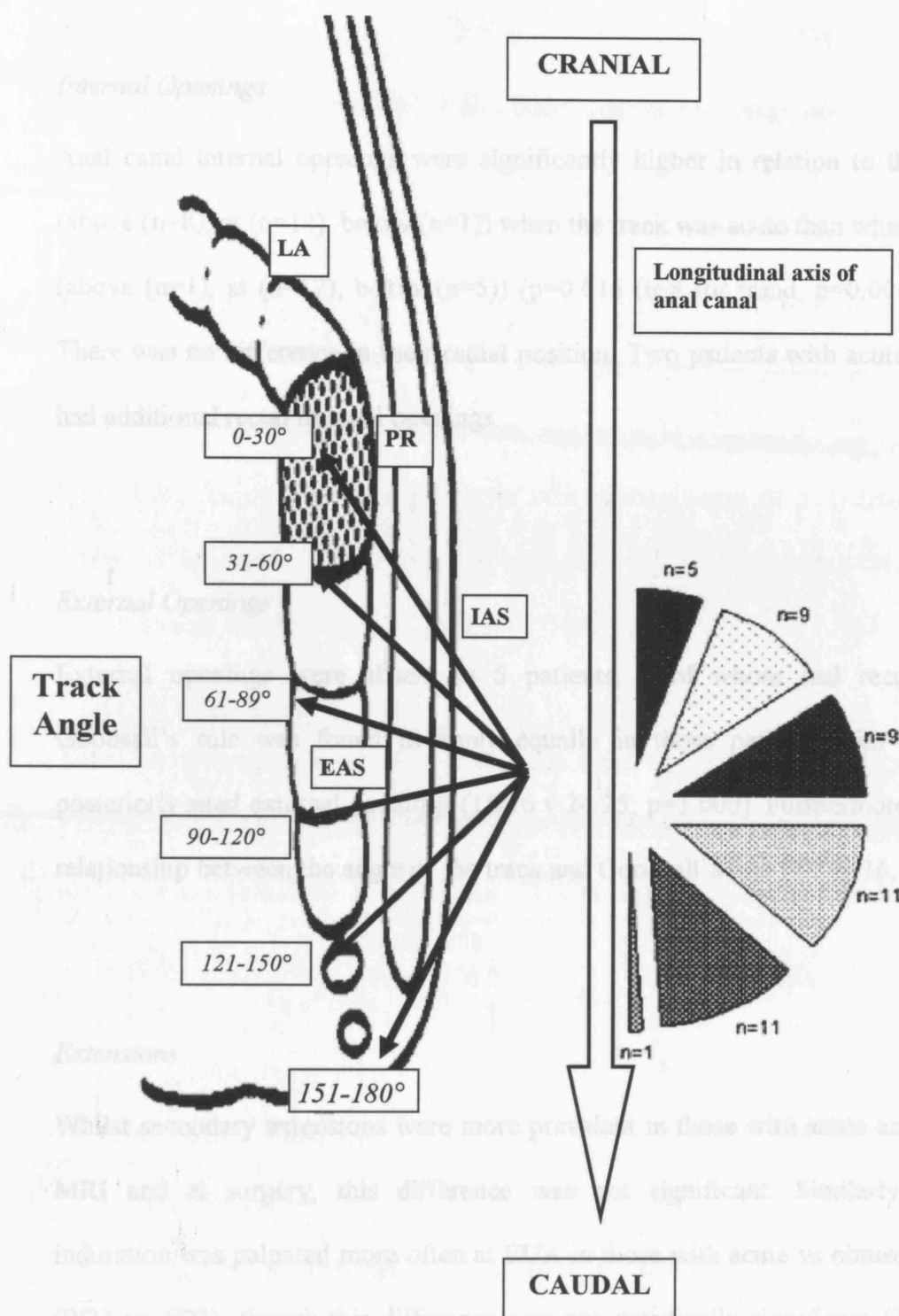


Figure 42: Distribution of angled tracks

The distribution of trans-sphincteric fistulas (right) tracking across the anal sphincter complex at different angles (left) in 46 patients. LA=Levator Ani; PR=Puborectalis; EAS=External anal sphincter; IAS=Internal anal sphincter

Internal Openings

Anal canal internal openings were significantly higher in relation to the dentate line (above (n=8), at (n=14), below (n=1)) when the track was acute than when it was obtuse (above (n=1), at (n=17), below (n=5)) ($p=0.015$ (test for trend, $p=0.004$)) (Table 16). There was no difference in their radial position. Two patients with acute angled tracks had additional rectal internal openings.

External Openings

External openings were absent in 5 patients, 3 of whom had recurrent disease. Goodsall's rule was found to apply equally in those patients with anteriorly and posteriorly sited external openings (15/16 v 24/25; $p=1.000$). Furthermore, there was no relationship between the angle of the track and Goodsall's rule (Table 16, page 181).

Extensions

Whilst secondary extensions were more prevalent in those with acute angled tracks on MRI and at surgery, this difference was not significant. Similarly, supralelevator induration was palpated more often at EUA in those with acute vs obtuse angled tracks (9/23 vs 4/23), though this difference was not statistically significant (Table 16, page 181).

Relationship between internal opening level and track angulation

Eight out of nine internal openings above dentate line level related to acute tracks extending cranially. Of these 9 high openings, 3 had acute tracks with angles of less than 30°, a further 3 had acute tracks angled between 31-60°, 2 had acute tracks angled between 61-90°, and the one obtuse track was angled at 91° to the longitudinal axis of the anal canal.

The fistula track crossed the sphincter at a median angle of 35° (range 14-91), 95° (range 30-165) and 131.5° (range 46-136) from internal openings sited above, at, and below dentate line level respectively (p=0.002).

Table 15: Demography of 46 patients with trans-sphincteric fistulas.

| Angle on MRI | Acute | Obtuse | p |
|--------------------|------------|------------|-------|
| Number of patients | 23 | 23 | |
| Age *: yrs | 43 (17-60) | 44 (21-65) | 0.169 |
| Male: female | 16:7 | 18:5 | 0.738 |
| Recurrent | 19 | 15 | 0.314 |
| Crohns | 2 | 2 | 1.000 |
| Number ops. * | 3 (0-18) | 3 (0-19) | 0.504 |

* = median

() = range

Table 16: Operative characteristics of 46 trans-sphincteric fistulas

| | | | | |
|---|-------|-----------------|-----------------|-------|
| Angle On MRI | | Acute | Obtuse | P |
| Number of patients | | 23* | 23 | |
| Suprlevator induration | | 9 | 4 | 0.189 |
| Level of internal opening in relation to dentate line | | | | |
| Anal canal | Below | 1 | 5 | 0.004 |
| | At | 14 | 17 | |
| | Above | 8 | 1 | |
| Rectum | | 2 | 0 | 0.489 |
| Radial position of anal internal openings | | | | |
| Anterior | | 5 | 7 | 0.792 |
| Lateral | | 2 | 2 | |
| Posterior | | 16 | 14 | |
| Site of external opening (relative to transverse anal line) | | | | |
| Anterior | | 7 | 9 | 0.667 |
| Posterior | | 14 | 11 | |
| Nil | | 2 | 3 | |
| Secondary extensions** | | | | |
| No | | 4 | 10 | 0.108 |
| Yes | | 19 ⁺ | 13 ^x | |
| Intersphincteric / Suprlevator | | 9 | 4 | 0.654 |
| Ischiorectal | | 18 | 11 | |

Values are numbers.

* Includes two patients with both extrasphincteric and trans-sphincteric primary tracks found on MRI and EUA

** Extensions shown by MRI and confirmed at EUA

⁺ , ^x Includes 8 and 2 patients respectively who had both intersphincteric/suprlevator and ischiorectal extensions.

Discussion

A trans-sphincteric fistula may be considered “high” when the internal opening lies above the level of the dentate line. However, the MRI data in this study suggests that half of trans-sphincteric fistulas track cranially through the sphincter complex, and that they are most acutely angled when their internal openings lie above the dentate line. Furthermore, almost one third of patients had tracks that were acutely angulated at less than 60°. In this circumstance fistulotomy will divide more sphincter muscle than would be appreciated from the level of the internal opening, which might precipitate faecal incontinence.

Body-coil MRI (chapter 3,4), which accurately classifies fistula-in-ano (Beets-Tan et al., 2001; chapter 5), was used to measure the angular relationship of trans-sphincteric fistulas relative to the longitudinal axis of the anal canal. To eliminate inter-observer variation, a single gastrointestinal radiologist, blinded to clinical findings, assessed all imaging, and was able to measure the angle in every case. Endo-anal MRI, using an endocoil, is invasive and may be uncomfortable for patients with perianal sepsis, but could demonstrate these findings more clearly due to the improved spatial resolution (Stoker et al., 1996). However, as there was no technical problem with measuring the angles from the body coil images, endocoil examination was not considered necessary.

Supralevator induration (Choen et al. 1991) may be indicative of supralevator sepsis, apical ischiorectal extension (Parks, Gordon, & Hardcastle, 1976) or a high trans-sphincteric fistula. Extensions and supralevator induration although more prevalent in acutely angled tracks were not statistically more common than with obtuse tracks. There

was difference in no demography or the radial site of internal openings demonstrable between acute or obtuse angled fistulas, and there was really no clinical sign to indicate the course of the track through the sphincter. Goodsall's rule states that a fistula associated with an external opening situated behind the transverse anal line will open into the anal canal in the midline posteriorly, whereas an anteriorly placed external opening is usually associated with a radial track. Goodsall's rule applied in almost all cases where an external opening was present in this study, but there was no relationship to the angle of the track.

It has been suggested that internal opening height does not always reflect the level at which trans-sphincteric fistulas cross the external anal sphincter (Thompson & Parks, 1979), although no anatomical basis for this observation has been determined. The cryptoglandular theory for the pathogenesis of fistula-in-ano has been accepted (Eisenhammer, 1958) generally, with infection of an anal gland in the intersphincteric space considered the initial event. Anal glands are usually situated at dentate line level (Seow-Choen & Ho, 1994), and only a small proportion actually penetrate the external anal sphincter. However, the glands may occasionally be sited cephalad or caudal to the dentate line (Eisenhammer, 1978; Hill, Shryock & Rebell, 1943). This might account for the internal openings noted in this study situated either above or below the level of the dentate line. Whilst the cryptoglandular theory holds true for the majority of fistula-in-ano, it must be recognised that many of these cases were tertiary referrals representing complex recurrent cases.

Eisenhammer hypothesized that fistulas result from sepsis tracking along fascial planes of least resistance. The intersphincteric space is really just a fascial plane between the

longitudinal layer (Williams et al., 2002) and the external sphincter. Trans-sphincteric fistulas may, therefore, track within this plane and later traverse the external sphincter through a further natural plane of cleavage (Fucini, Elbetti & Messerini, 1999)

Although the EAS may function as a single component, there has been much debate about its structure. Whilst some authors consider it a single entity (Goligher, Leacock & Brossy, 1955) current nomenclature is based on a tripartite structure with deep, superficial and subcutaneous parts (Milligan & Morgan, 1934). Despite further studies suggesting that the deep EAS and puborectalis are continuous and share the same innervation (Barranger, Haddad, & Paniel, 2000; Shafik, 1975; Shafik, 1987), investigators have recently demonstrated an important plane of separation between these two components (Fucini, Elbetti, & Messerini 1999). This plane could act as a conduit for sepsis to track into the ischiorectal fossa, and may explain the group of fistulas with high internal openings and acutely angled tracks. Those fistulas passing caudally through the sphincter complex may likewise pass through the junction between the superficial and subcutaneous components, along a plane of interlacing fibres from the longitudinal layer (Lunniss & Phillips, 1992)

Inexperienced probing (Lewis, 1996) may lead to iatrogenic track formation when the internal opening has been hard to demonstrate (Abcarian, 1996; Finlay, 1996; Parks, Gordon, & Hardcastle 1976). Preoperative imaging may help to prevent this by depicting the complete anatomical pathway of the fistula (Hwang & Chen 1996; Ratto et al., 2000). In this present study, two patients with acute angled trans-sphincteric fistulas, which could not be negotiated by probing at EUA, had additional extrasphincteric tracks. Both were recurrent cryptoglandular fistulas, and it was

presumed that the extrasphincteric tracks were iatrogenic due to injudicious probing at previous surgery. Lockhart Mummery probes will usually traverse linear or slightly curved fistulas (Hawley, 1975), however tracks which are very angulated, possibly in multiple planes, may prove impassable, and continued forceful probing would then lead to an iatrogenic tracks or false passage into the rectum if probing is directed towards the roof of the ischiorectal fossa (Parks, Gordon, & Hardcastle, 1976). Alternative strategies, including core-out fistulectomy (Lewis, 1996) or the use of a radial circumferential incision to facilitate access, should be used instead to demonstrate the true pathway of the fistula.

In summary, approximately half of trans-sphincteric fistulas angle cranially through the sphincter complex from their internal opening, and are most acutely angled when the internal opening lies above the dentate line. These findings have important implications in the surgical treatment of trans-sphincteric fistula-in-ano. Preoperative MRI should be performed in all cases of recurrent fistula-in-ano (chapter 3). In addition, where internal openings seem high on preoperative assessment, MRI may be useful in alerting surgeons to potentially hazardous probing and fistulotomy.

Chapter 9:

**Sphincter conserving fistula surgery
– Traditional approaches**

Literature review

This literature review of traditional of sphincter conservation is followed by a long-term appraisal of the loose-seton technique.

Core out

Core-out fistulectomy involves complete fistula excision from the cutaneous perineal surface to the internal opening. The advantages for “high” tracks include accurate visualisation of both primary and secondary tracks, avoidance of probing or developing false tracks, enabling histological assessment of the track and the ability to depict the level of the track relative to the sphincter before dividing any muscle (Lewis, 1996).

Core-out fistulectomy may be combined with simple internal opening closure (Lewis, 1986), seton placement (Ustynoski et al., 1990) or mucosal advancement flap (Stone & Goldberg, 1990). Lewis (1986) described 2 recurrences in 100 low fistulas and 1 from 18 high trans-sphincteric or suprasphincteric fistulas treated in this manner. Similarly, Christiansen and Ronholt (1995) reported 2 recurrences in 14 patients, with only 3 patients reporting minor faecal incontinence (Figure 43, page 188).

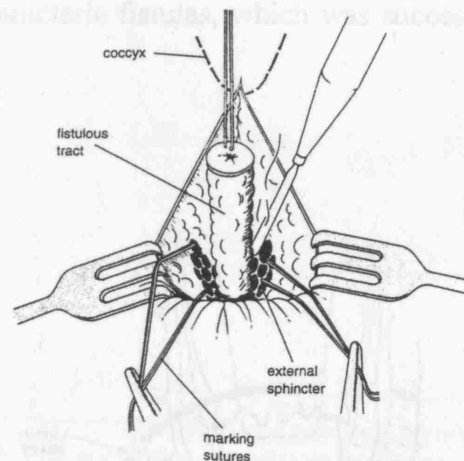


Figure 43: Core out fistulectomy with isolation of fistulous track and sphincter division between bundles

Christiansen J & Ronholt C 1995, Treatment of recurrent high anal fistula by total excision and primary sphincter reconstruction, *Int.J Colorectal Dis.* **10**: 207-9. (Reproduced with kind permission from authors and Springer©)

Advancement flap

Advancement flaps can be employed to cover the internal fistula opening after excision and or curettage of the intersphincteric tracks and any tracks lateral to the sphincter complex. Some authors additionally leave a drain through the external opening (Shemesh et al., 1988). Flaps are usually employed where definitive cure of a fistula is sought, though fistulotomy might compromise function.

While the size of the flap, both circumferentially and longitudinally can vary (Berman, 1991), it is important to ensure that the base of the flap is wider than its apex. In essence there are two main types; anocutaneous flaps describe a mobilised flap of skin advanced cranially into the anal canal, and trans-anal or endorectal flaps (Stone & Goldberg, 1990; Jones et al., 1987) (Figures 44-47, pages 189,190) advance a mobilised flap of anorectal tissue caudally over the defect. Pescatori et al (1995) even report a double flap using a combination of the two techniques. Pinedo and Phillips (1998) have described the addition of a labial fat pad graft (Martius) in patients with complex

rectovaginal and suprasphincteric fistulas, which was successful in 6 out of 8 cases in the medium-term.

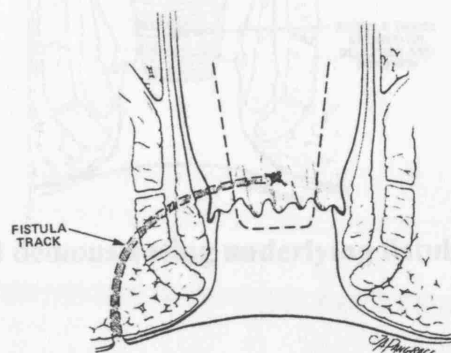


Figure 44: Anorectum indicating site of anterior rectal advancement flap

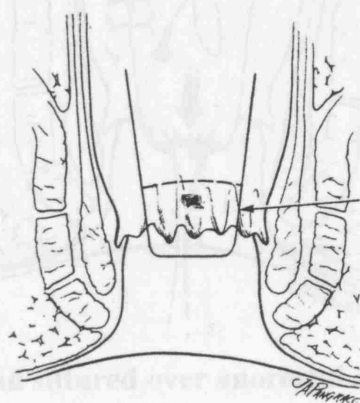


Figure 45: Rectal advancement flap raised. Apex of flap incorporating fistula orifice to be excised (arrow)

Whilst the size of the flap, both circumferentially and longitudinally can vary (Berman, 1991), it is important to ensure that the base of the flap is wider than its apex (Zimmerman, Briel, & Schouten 2001). Anocutaneous flaps usually do not involve the division of any muscle, however the endorectal flap usually consists of internal sphincter as well as mucosa and submucosa. Usually muscular defects are closed prior to flap suturing.

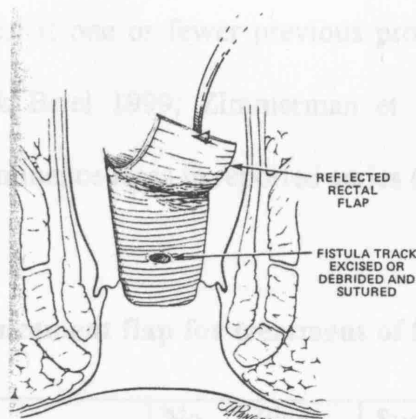


Figure 46: Flap reflected demonstrating underlying fistula

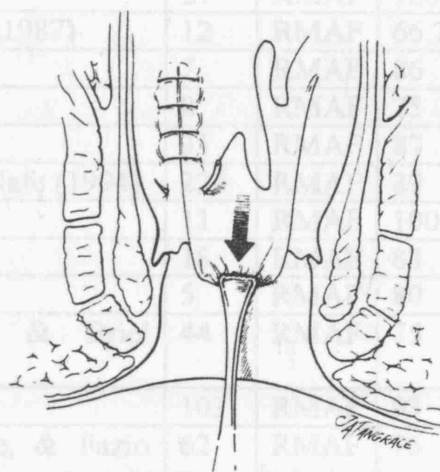


Figure 47: Flap advanced and sutured over anorectal defect

(Figs 44-47 reproduced with kind permission from authors (Jones IT Fazio VW & Jagelman DG 1987 The use of transanal rectal advancement flaps in the management of fistulas involving the anorectum *Dis.Colon Rectum* 30: 919-923) and Springer©

Functional outcome is reported as very good in 22 out of 24 patients studied by Kreis et al (1998). Some report that long-term success is similar in those with cryptoglandular and Crohn's fistulas (Ozuner et al., 1996), whilst others have found Crohn's predictive of flap failure (Mizrahi et al. 2002; Sonoda et al. 2002). Furthermore, smoking (Zimmerman et al. 2003) has a deleterious effect on success. Recurrence has been observed from 15 months to 5 years (Ozuner et al., 1996; Sonoda et al., 2002) after the procedure. Zimmerman et al found that anocutaneous and transanal techniques were

more likely to be successful if one or fewer previous procedures had been employed (Schouten, Zimmerman, & Briel 1999; Zimmerman et al. 2001). The table below illustrates success and incontinence rates in reported series (Table 17, below).

Table 17: Success of advancement flap for treatment of fistula-in-ano

| Author and year | No. | Flap type | Success (%) | Incontinence (%) |
|---|-----|-----------|-------------|------------------|
| Oh (1983) | 15 | RMAF | 87 | Not stated |
| Aguilar et al. (1985) | 21 | RMAF | 98.5 | 10 |
| Wedell et al. (1987) | 27 | RMAF | 100 | 0 |
| Jones, Fazio, & Jagelman (1987) | 12 | RMAF | 66.7 | Not stated |
| Reznick & Bailey (1988) | 7 | RMAF | 86 | 0 |
| Lewis & Bartolo (1990) | 8 | RMAF | 75 | 12.5 |
| Kodner et al. (1993) | 31 | RMAF | 87 | Not stated |
| Athanasiadis, Kohler, & Nafe (1994) | 224 | RMAF | 89 | 21 |
| Lewis et al. (1995) | 11 | RMAF | 100 | 0 |
| Miller & Finan (1998) | 18 | RMAF | 83 | 0 |
| Hyman (1999) | 5 | RMAF | 80 | 0 |
| Schouten, Zimmerman, & Briel (1999) | 44 | RMAF | 75 | 35 |
| Ortiz & Marzo (2000) | 103 | RMAF | 93 | 8 |
| Sonoda, Hull, Piedmonte, & Fazio (2002) | 62 | RMAF | 76 | Not stated |
| Gustafsson & Graf (2002) | 34 | RMAF | 59 | Not stated |
| Del Pino et al. (1996) | 8 | AC | 88 | Not stated |
| Robertson & Mangione (1998) | 14 | AC | 78 | 7 |
| Jun & Choi (1999) | 40 | AC | 98 | 0 |
| Nelson, Cintron, & Abcarian (2000) | 53 | AC | 74 | Not stated |
| Zimmerman, et al. (2001) | 26 | AC | 46 | 30 |
| Amin et al. (2003) | 18 | AC | 83 | 0 |

RMAF=rectal mucosal advancement flap

AC = anocutaneous advancement flap

Seton

Setons were described in the writings of Hippocrates and John of Arderne (Corman, 1980). Since then chemical, tight / cutting or loose seton techniques have been widely

employed. Series are difficult to compare, as authors usually have different methods or study heterogeneous groups.

Chemical seton

Chemical setons, widely used in Asia, provide a non-operative ayurvedic method of treating fistula-in-ano. The seton, which is strongly alkaline, is passed along the fistula track. Its caustic action provides anti-bacterial properties, as well as burning granulation tissue. In a randomised control trial involving over 500 patients, healing times were longer than conventional surgery (Shukla NK et al 1991), however both recurrence and incontinence rates were lower. In a subsequent randomised control trial for patients with low fistula-in-ano, Ho et al (2001) reported no difference in either healing rates or function when comparing fistulotomy and chemical seton, however the latter technique was more painful in the short-term. Whilst chemical setons clearly provide a unique drug delivery system, they have not found worldwide usage due to licensing issues.

Tight seton

Tight (or cutting) setons are thought to act through slow transection of the enclosed sphincter muscle (McCourtney & Finlay, 1995), the subsequent tissue fibrosis is thought to prevent the sphincter from springing apart, therefore minimising any functional disturbance. Cutting setons may periodically need tightening although some primarily cut through (Lentner & Wienert, 1996).

Culp (1984), who reported a retrospective series of 20 patients with complex fistula-in-anus where a Penrose drain was used as a primary operative seton, postulated that the seton caused pressure necrosis and allowed abscess drainage. The median time for this drain to cut through was 14 days, and there was minimal continence disturbance (3 of 20 patients), however fistula classification was not described. Other materials employed as setons include stainless steel wire (Misra & Kapur, 1988), elastic bands (Hanley, 1978) and nylon (Kuypers, 1984).

Christensen (1986) recorded functional deficit in 13 of 21 (62%) patients who were assessed at a median of eight years after tight seton placement for high trans-phincteric fistulas; whilst none had recurrent sepsis, anal deformity was highly predictive of continence disorder. Hamalainen and Sainio (1997) similarly found anal guttering associated with incontinence, also reporting that 18 of 35 patients re-examined reported new minor control defects at an average of 70 months postoperatively.

Ustynoski et al (1990) described the use of multiple setons placed through counter incisions to drain horseshoe sepsis, and found this technique useful to drain the deep postanal space, whilst simultaneously gradually tightening a seton in outpatients through the primary track. They emphasised the importance of dividing the overlying skin and anoderm to enable painless treatment.

McCourtney and Finlay (1996) reported good functional outcome in their series of patients treated by cutting seton where the internal sphincter was preserved. They argued, that whilst internal sphincterotomy was believed necessary by many authors before cutting seton placement this might provoke incontinence. Isbister and Sanea

(2001) reported flatus incontinence in 10% of 47 patients with trans-sphincteric fistulas treated by cutting seton.

Some employ a Rubber Band Ligator to tighten cutting setons (Cirocco & Rusin 1991; Thomson, 1995), whilst others pass a new seton through a loop tied in the knotted suture (Soew-Cheon & Leong, 1994) or even use a “hangman’s tie” (Loberman et al. 1993; Schein 1995). Some use a looped seton from the outset (Jain & Gupta 1995).

An alternative technique is two-stage seton fistulotomy (TSSF). This involves loose seton placement to mark the track, which proponents believe stimulates fibrosis, and fistulotomy performed as a delayed second procedure. Often a proximal partial EAS sphincterotomy is performed, along with division of the perianal skin and underlying IAS, followed by delayed division of the caudal EAS (Parks & Stitz 1976; Pearl et al. 1993).

Van Tets and Kuypers (1995) described a technique of TSSF involving internal sphincterotomy and distal EAS division, with tight seton placement around the residual proximal EAS. This latter muscle was divided at a second later procedure. All of these patients had high anal or rectal internal openings. On follow-up, 17 out of 29 patients who had normal preoperative faecal control had impaired postoperative continence.

Garcia-Aguilar et al (1988) found that TSSF and cutting seton were equivalent in eradicating the fistula, however both techniques rendered equally high numbers of patients incontinent (31/47 vs 8/12).

Loose seton

Some surgeons use a seton to drain fistula *in ano* (Thomson & Ross 1989), whereas others believe that seton placement stimulates fibrosis and therefore promotes healing (Parks & Stitz, 1976). When a seton is used to mark the primary track (Culp, 1984; Lunniss & Thomson, 1996) the subsequent decision whether or not to lay the fistula open can be made easier by palpating the seton in relation to the anal sphincter complex (Hawley, 1975). Further, long-term seton placement can help drain fistula in patients with AIDS (Pearl et al., 1993) and Crohn's disease (White et al., 1990). Faucheron (1996) studied 41 Crohn's patients with high anal fistulas, of whom eleven were treated by permanent long-term seton drainage, whilst the other 30 had setons placed as part of staged treatment. As many (those who had successful flap or seton removal) did not require fistulotomy, Faucheron concluded that this approach could help preserve anal musculature. More recently, seton placement combined with Infliximab and maintenance immunosuppressives has been useful in Crohn's fistula-in-ano, with 14 of 21 (67%) healed at a mean follow-up of 9 months (Topstad et al. 2003). Whilst these results might sound impressive, clinical response was classified as cessation of fistula drainage, which may in actuality not represent eradication of the track. Further work in this area is required.

The loose seton technique presents an alternative technique, and although short-term results are impressive (Kennedy & Zegarra 1990; Lunniss & Thomson 1996; Thomson & Ross, 1989; Williams et al., 1991), long-term results which are currently unknown are studied in this chapter below.

Intersphincteric approach

Matos et al. (1993) described a technique aimed at preserving the whole sphincter complex. This consisted of an intersphincteric dissection to eradicate intersphincteric sepsis, internal opening suture from within the intersphincteric space, together with core-out and primary repair of the tracks through and lateral to the EAS. In 13 patients with complex trans-sphincteric and suprasphincteric fistulas, complete success was reported in 7, partial success in 2 where internal sphincterotomy was later required to permit healing, and complete failure in 4, at a mean medium-term follow-up of 22 months. No long-term data is available for this technique.

Soave

This technique, involving rectal excision followed by coloanal pull through and anastomosis, is applicable in treating pelvic sepsis associated with extrasphincteric fistulas without loss of anal sphincter musculature. The anastomosis is constructed caudal to the infected field, and as the colon acts as a vascularised graft healing inevitably takes place. Maxwell-Armstrong and Phillips (2003) found that all 5 of their cases healed, with satisfactory functional results, and suggested that this technique might be applied where local treatments have failed.

Re-routing the fistula track

Mann and Clifton (1985) reported this sphincter preserving technique for high anal and anorectal fistula in 5 patients, where no colostomy was required. All had complex fistulas, two were suprasphincteric and three trans-sphincteric of whom one also had an

extrasphincteric track. Excellent results were obtained, with no deterioration in continence or recurrence 9 months following surgery, however long-term data are not available.

The track is cored-out from the external opening up to the point where it crosses the EAS or puborectalis. Using saline and adrenaline infiltration, the intersphincteric plane is dissected up to the track and the external portion of the fistula is then passed through the hole into this plane, if necessary enlarging the hole in the EAS or puborectalis. A seton, already placed through the primary track, facilitates this dissection. The EAS defect is repaired, and after 2-3 weeks when external wounds have healed the IAS below the primary track is divided after cranial retraction of the mucosa, hence “swinging” the track into the submucous plane, where it can usually be excised. If the track is very high this last stage is performed after the IAS has been repaired and again healed following a 3-week period.

Combination treatment

Whilst many treatments are outlined above, a combination of modalities is usually employed, particularly in complex fistula-in-ano. For instance the first operation may involve lay-open of secondary tracks and loose-seton placement, with delayed tight seton / advancement flap / lay open of the main track.

Long-term outcome following the loose-seton technique for external sphincter preservation in complex anal fistula

Introduction

Fistula-in-ano is commonly treated by fistulotomy. This technique eradicates intersphincteric infection by dividing the epithelium and anal sphincter musculature overlying the fistulous track and the diseased intersphincteric anal gland, hence permitting healing by secondary intention. It cures most simple intersphincteric tracks with minimal functional disturbance following IAS division (Lunniss, Kamm, & Phillips, 1994). Partial or complete EAS division for complex trans-sphincteric, suprasphincteric and extrasphincteric fistulas may precipitate worsening degrees of faecal incontinence (Cavanaugh, Hyman, & Osler, 2002). In this circumstance, sphincter-conserving treatments including internal opening closure (Reznick & Bailey, 1988), fistula track rerouting (Mann & Clifton, 1985), use of advancement flaps (Ortiz & Marzo 2000) or fibrin sealant (Park et al., 2000), core-out fistulectomy (Schouten & van Vroonhoven, 1991), and cutting (Hamalainen & Sainio, 1997) or permanent loose-seton placement, are often advocated.

An alternative technique, which preserves the integrity of the EAS and is a modification of that reported by Parks and Stitz (1976), involves loose-seton placement and subsequent removal after the successful eradication of secondary tracks and acute sepsis. Although short-term success rates of between 44 and 86 per cent have been reported (Kennedy & Zegarra, 1990; Lunniss & Thomson, 1996; Thomson & Ross, 1989; Williams et al., 1991), long-term results are unknown. This study assessed the long-term success of the loose-seton technique (LST) as a sphincter-conserving

treatment for complex fistula in ano by undertaking follow-up of a consecutive cohort of patients whose short-term results had been assessed previously (Lunniss & Thomson, 1996).

Patients and methods

This study aimed to assess the long-term clinical result of the LST at a minimum of 10 years after surgery. A consecutive series of 24 patients with fistula-*in-ano* who had been treated by the LST at St. Mark's hospital between March 1990 and August 1991 was studied.

The early outcome of the original 24 patients has been summarized previously (Lunniss & Thomson, 1996). Two patients were subsequently lost to follow-up, another with a persistent fistula was shown to have adenocarcinoma within fistula curettings, and a further patient died from unrelated disseminated malignancy shortly after the original report. These four patients were excluded from further analysis. Twenty patients were therefore studied by case-note review, supplemented by mailed and telephone interview (eight patients). Although 14 of these patients had cryptoglandular fistula *in ano*, six had Crohn's disease either at the time of the original surgery or subsequently diagnosed during follow-up.

There were three women and 17 men, of median age 41 (range 24–70) years. Patients had had clinically proven fistula *in ano* for a median of 27 (range 1–240) months before this treatment. All but one patient with a primary fistula had recurrent disease; the median number of previous operations was 3 (range 0–13). All 19 patients with recurrent fistulas were tertiary referrals from other hospitals, and the nature of any

previous fistula surgery was therefore difficult to ascertain. All 20 patients had a complex fistula according to the primary track classification; there were 18 trans-sphincteric and two suprasphincteric fistulas (Marks & Ritchie, 1977). The internal opening was posterior in 16, anterior in one and lateral in three patients. Nine of these openings were situated above the dentate line and 11 at the level of the dentate line.

The LST (Kennedy & Zegarra, 1990; Lunniss & Thomson, 1996; Thomson & Ross 1989) included an initial examination under anaesthetic at which secondary extensions were identified and laid open. The intersphincteric space was laid open by division of the IAS and overlying epithelium, from the level of the primary track to the anal verge, eradicating the affected anal gland. A loosely tied no. 1 nylon seton was then placed to encircle the remaining EAS.

Patients initially underwent a median of 3 (range 2–7) procedures under anaesthesia. Besides seton placement, laying open of seven supralelevator abscesses and 12 ischiorectal horseshoe extensions was carried out, and further inspections were often required to ensure that these cavities were adequately drained. Subsequently, wounds were treated by digitation and irrigation, until sepsis was quiescent and there were good signs of healing both in the laid-open wounds and in the track around the seton. Only then was the seton removed as an outpatient procedure, at a median of 13 (range 3–28) weeks after its initial placement. Patients were followed up in the short term for a median of 6 (range 2–24) months after seton removal.

Long-term follow-up was undertaken at a median of 142 (range 125–153) months after seton removal. All case notes were reviewed to ascertain whether any patient whose

fistula had remained healed at short-term follow-up had required further unplanned surgery. Where necessary, patients were contacted by telephone or letter.

Statistical analysis

The success of the LST was defined as complete eradication of sepsis following seton removal. Comparisons were made between results obtained at short- and long-term follow-up. Categorical frequencies were analysed using Fisher's exact test. Analysis was performed using Arcus Quickstat Biomedical version 1.2 (Research Solutions, Cambridge, UK). Statistical significance was assigned at the 5 per cent level.

Results

Results are summarized in Table 18 (page 202) . After seton removal, the median interval to complete healing was 9 (range 1–44) weeks in 16 of the 20 patients. At short-term follow-up four patients had either evidence of a persisting fistula or a wound that had not completely healed; none of these patients required further surgery during this period. Three of the 16 patients whose fistula healed initially on seton removal underwent laying open of the EAS below the level of the primary track owing to further evidence of sepsis. Therefore, at short-term follow-up, 13 of 20 fistulas had healed completely.

Table 18: Short versus long-term outcome of the loose-seton technique for fistula-in-ano in 20 patients

| <i>Median follow up</i> | <i>Short term 6 months</i> | <i>Long term 142 months</i> |
|---|--------------------------------|---------------------------------|
| Complete healing without additional surgery | 13 | 4 |
| Lay open of external sphincter to heal | 3 | 7* |
| Lay open of extension to heal | 0 | 2 |
| Permanent loose seton placed | 0 | 4 |
| Persistent fistula | 4 | 3 |

* Includes one patient who underwent fistulotomy when advancement flap failed

On long-term follow-up, two of the four patients whose fistulas had remained unhealed on short-term follow-up developed recurrent sepsis, necessitating permanent loose-seton placement in one and fistulotomy of the residual caudal EAS in the other. Although the other two still had clinical evidence of a fistula, their symptoms were minimal, and neither required further surgery.

Of the 13 patients whose fistula had remained healed in the short term, two subsequently required drainage of persistent secondary extensions (one ischiorectal, one intersphincteric), and six developed recurrent sepsis due to a persistent primary track through the EAS in the long term. In three of these six sepsis was controlled by the placement of a permanent loose seton and one had an advancement flap that subsequently failed. The latter patient and two others underwent fistulotomy of the remaining EAS below the primary track, with successful resolution of sepsis in the long

term. One of the 13 patients developed a persisting fistula that caused minimal symptoms, and again was not keen to undergo further surgery. Therefore, four patients remained completely healed and required no further surgery in the long term. None of the three patients who had initially undergone fistulotomy in the short term suffered a relapse. All additional unplanned surgery was carried out at this institution, except for drainage of a persistent ischiorectal extension at a local hospital in one patient.

In the long term, EAS division was necessary to control sepsis in seven of 20 patients compared with three of 20 at short-term follow-up. Altogether, the long-term success rate of the LST for completely eradicating sepsis due to complex fistula *in ano* was lower than that noted on short-term follow-up (four *versus* 13 of 20). Five of the six fistulas associated with Crohn's disease, and 11 of 14 associated with cryptoglandular fistula *in ano* eventually recurred ($P = 1.000$). No patient with Crohn's disease required proctectomy to eradicate sepsis in the long term.

The success rate of the LST in completely eradicating sepsis fell with time. The fistula had recurred in seven, 11 and 15 patients at 6, 15 and 60 months following seton removal respectively; relapse in one patient was noted 76 months after the initial treatment (Figure 48, page 204). All recurrences were in the same plane and radial location as the initial fistula.

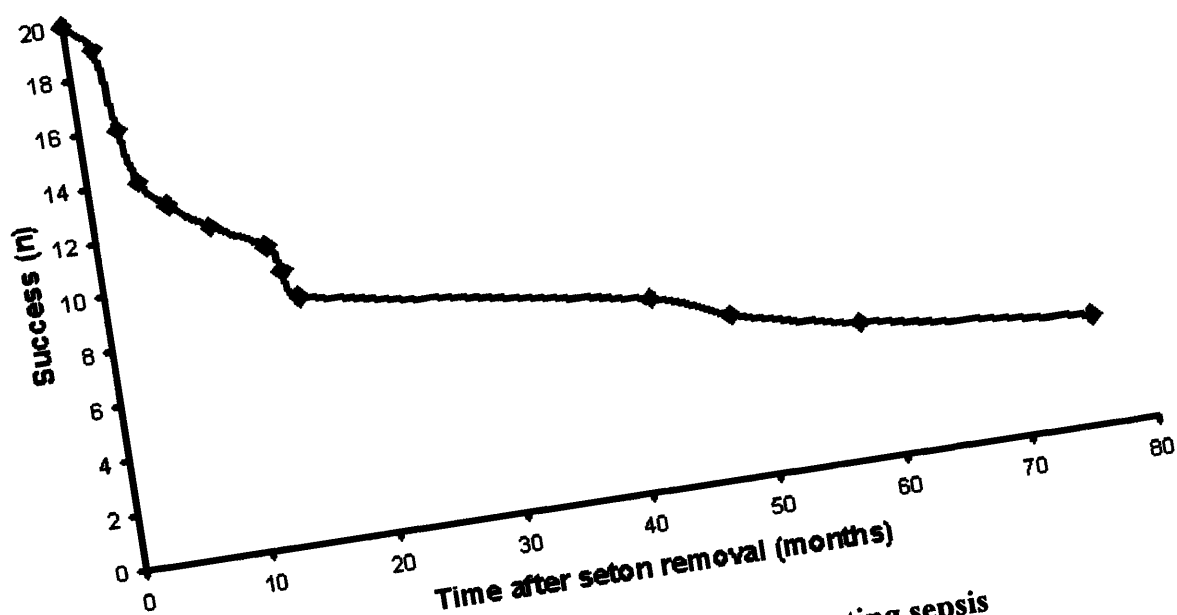


Figure 48: Success of the loose seton technique in eradicating sepsis over time in 20 patients
 Number of patients at risk for each point displayed above, are contained in grid below.

| Time (months) | 0 | 2 | 3 | 4 | 6 | 9 | 13 | 14 | 15 | 42 | 48 | 58 | 76 |
|--------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|
| No. at risk | 20 | 19 | 16 | 14 | 13 | 12 | 11 | 10 | 9 | 7 | 6 | 5 | 4 |
| Total no. relapsed | 0 | 1 | 4 | 6 | 7 | 8 | 9 | 10 | 11 | 13 | 14 | 15 | 16 |

Discussion

Complex fistulas usually have a primary track that crosses the EAS. This may be acutely angulated and associated with a high internal opening (see chapter 8). The presence of any additional secondary extensions can make eradication of sepsis challenging. Fistulotomy is often inadvisable because of the proportion of the anal sphincter complex lying beneath the primary track, so sphincter-conserving therapies such as the LST are often employed.

Initial reports suggested that loose-seton placement allowed preservation of the EAS in nearly half of patients with complex trans-sphincteric fistulas (Thomson & Ross, 1989), patients in whom sepsis was eradicated by this method reported significantly better postoperative continence than those in whom delayed EAS division enabled healing, some of whom even required later anal sphincter repair. Similarly, healing was reported in 25 of 32 patients with high trans-sphincteric and suprasphincteric fistulas, with minimal changes in continence at a mean follow-up of 36 months (Kennedy & Zegarra, 1990). Williams *et al.* (1991) reported 14 patients whose fistulas all healed following seton removal at a median of 10 weeks; however, relapse was noted in two at median of 24 months' follow-up.

In the present study, fistulas in 13 of 20 patients were healed at short-term follow-up after treatment with the LST. However, assessment after 10 years revealed an increased number of relapses, with complete healing in only four of 20 patients. Although this cohort is small, it adds to the few available data on the LST, including information on long-term outcome. When relapse was evident, simple abscess drainage or further loose-seton placement often enabled EAS preservation. Some patients even preferred to live with minor symptoms from the fistula rather than face additional surgery. As functional data were not recorded at the time of initial treatment, function was not formally assessed in the long term.

Nineteen of 20 patients in this cohort had recurrent fistula, in comparison to eight of 34 patients reported by Thomson and Ross (1989). Furthermore, almost one-third of the present patients had Crohn's disease, a condition specifically excluded in the study reported by Kennedy and Zegarra (1990). As such, the present cohort represents a

particularly challenging group to treat, which may explain differences in success rates in comparison to those of other series. This study also reflects the importance of long-term assessment of surgical techniques. It is interesting to note, however, that there was no difference in recurrence rate among patients with Crohn's disease and those with cryptoglandular fistula *in ano* in the present study, although the numbers were small. Furthermore, no patient with Crohn's disease required proctectomy in the long term. Patients with a Crohn's fistula often have more than one primary track, and a proportion have co-existing proctitis, so judicious seton placement to control sepsis (Scott & Northover, 1996) may postpone the need for major surgery (White et al., 1990).

Parks and Stitz (1976) described a technique for treating high fistulas that partially preserved the EAS through loose-seton placement; residual EAS division was necessary in only 38 per cent and, not surprisingly, this latter group reported worse postoperative function. The technique of two-stage seton fistulotomy (TSSF) has been associated with a high degree of incontinence, especially when the internal opening is high (Van Tets & Kuijpers, 1995). However, direct comparison of use of cutting setons and TSSF to treat high fistula-*in-ano* found no differences between the two methods in either eradicating sepsis or preventing incontinence (Garcia-Aguilar et al., 1998). Avoidance of incontinence is the strongest argument in favour of anal sphincter conservation, even when success rates are poor compared with those of fistulotomy, as patient dissatisfaction is strongly associated with incontinence following fistula surgery (Garcia-Aguilar et al., 2000).

In summary, although temporary seton placement is a useful initial step in the management of complex fistula-*in-ano*, its success rate falls over time and this method

cannot therefore always provide definitive treatment. Counselling before seton removal must emphasize that, although most patients do not require EAS division and some are cured using this technique, many patients develop further sepsis that will necessitate additional surgery.

Chapter 10:

Sphincter conserving fistula surgery – Novel approaches

Literature review

Novel minimally invasive techniques for sphincter conservation are described below, followed by a prospective study assessing the efficacy of fibrin sealant treatment.

Carbon dioxide laser

Slutzki et al (1981) reported three cases where the fistula was cored out using a carbon dioxide laser. The laser had a focus-guide emitting red light, which permitted visualisation of its path and helped prevent damage to the rectum. The internal opening was left to heal without closure, though a paraffin gauze rectal pack was placed. At short-term follow-up, 5 months after treatment, no recurrence or altered continence was described, however long-term data is not available.

Fibrin sealant

The concept of using sealant to plug a fistula is an attractive idea. Cyanoacrylate based adhesives do not provide an interlacing fibrin network, unlike fibrin sealant and merely seal tissues together. They tend to be used for minor skin wound closure and additional suture support. Fibrinogen has been used as an adjunct for surgical haemostasis for over a century, however it was first employed as a tissue adhesive in the 1940's (Sierra, 1993). Improvements in sealant strength, largely due to increased fibrinogen concentrations obtained using cryoprecipitation techniques, have led to applications including haemostasis, tissue sealing and fistula sealing.

Fibrin sealants are tissue adhesives derived from blood, which mimic and speed up the last steps of the coagulation cascade, generally consisting of two component solutions (Figure 49, page 210):

- component 1: fibrinogen (human), together with factor XIII
- component 2: thrombin (human or bovine), together with calcium chloride

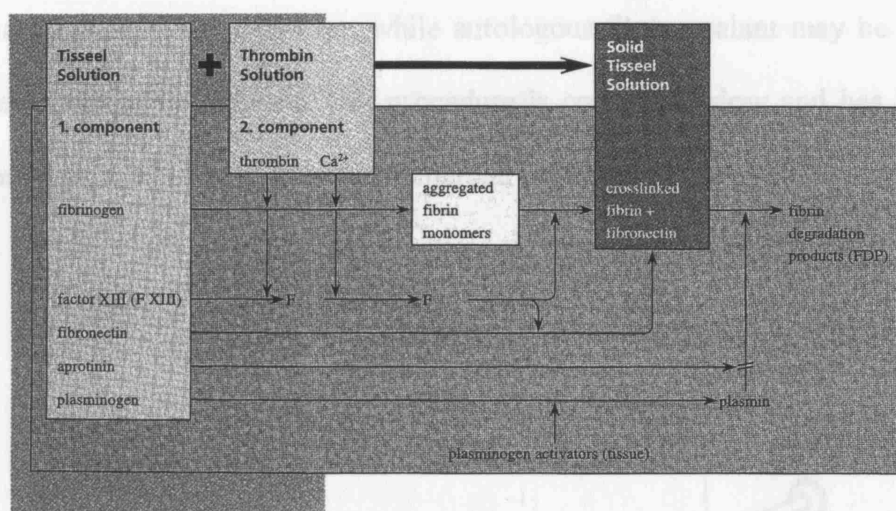


Figure 49: Components of fibrin sealant

Mixing of these during application causes sealant formation. Sealant adheres to many surfaces including exposed collagen and remains in vivo for several days, aided by the addition of an anti-fibrinolytic agent such as aprotinin. After this time it is absorbed by enzymatic and phagocytic mechanisms. As fibrin sealant sets, interlacing fibrin strands form a fibrin mesh, and thus provide the natural environment for unimpeded fibroblast proliferation, and hence wound healing. Sealant also acts as a plug, therefore preventing contamination.

Literature Review: Fibrin sealant for anal fistula

The most commonly used application system for fibrin sealants is the Duploject double syringe system (Figure 50, page 211), however sealants may also be applied as an

aerosol spray. The contents of the two syringes are released at the same time and mixed in the Y-piece of the syringe, where polymerisation is initiated, and in this way fibrin sealant can be directly applied to the site. Commercially available fibrin sealants utilise human pooled fibrinogen, and are, like all blood products, carefully screened for viral contaminants. However, as some sealants contain bovine products, concern over risks of bovine spongiform encephalopathy and antigenic reactivity (Hughes & Westwood, 1994), led many investigators to use autologous sealants while FDA approval was temporarily withdrawn. However, while autologous fibrin sealant may be prepared by cryoprecipitating whole blood, this procedure is costly and slow and has largely been abandoned since FDA reapproved commercial products.

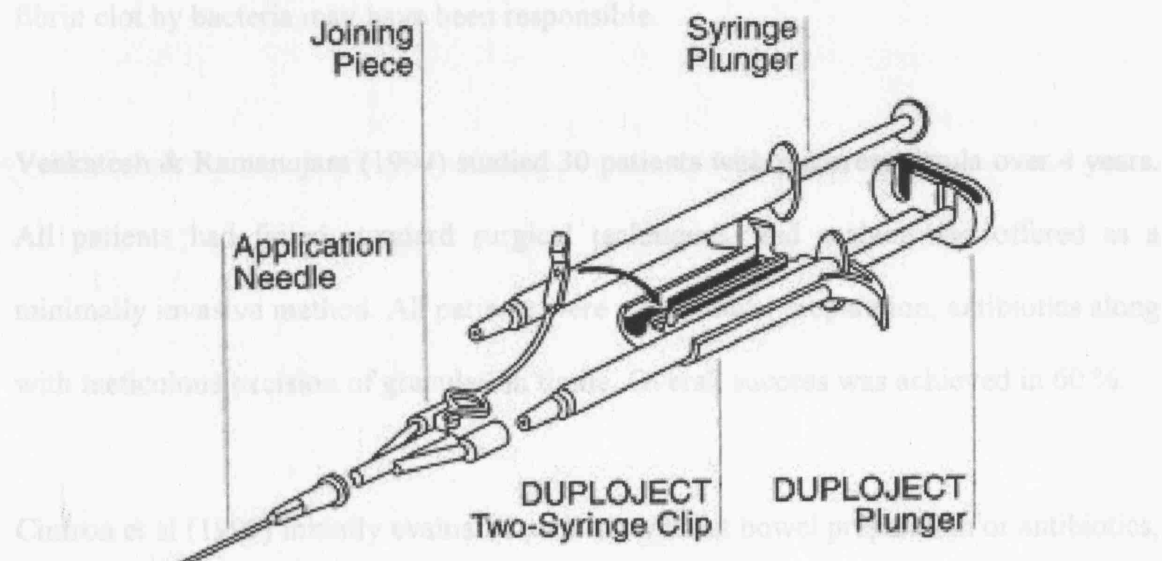


Figure 50: Duploject syringe used to apply fibrin sealant

Literature Review: Fibrin sealant for anal fistula

Hjortrup et al (1991) first described the use of fibrin sealant in the treatment of fistula-in-ano. They used preoperative fistulography, a technique now recognised to be

inaccurate, to exclude patients with secondary extensions. Their technique involved excision of all granulation tissue using a curette, track irrigation with antibiotics which was altered according to sensitivities, before going on to instill commercial fibrin sealant 3 days later. Healing occurred in 6 out of 8 patients, however some needed up to three attempts. Mechanism of follow-up and assessment of healing was not disclosed.

Abel et al (1993) used autologous fibrin sealant in 5 patients. All had mechanical bowel preparation and preoperative antibiotics, however only 2 fistulas healed. They advised against sealant in those with Crohn's or HIV related fistulas. Despite these early encouraging results, Aitola et al (1999a) using commercial sealant found that none of 10 fistulas healed, despite meticulous track preparation and antibiotic administration. Some fistulas even recurred after initial skin healing, and they hypothesised that lysis of the fibrin clot by bacteria may have been responsible.

Venkatesh & Ramanujam (1999) studied 30 patients with recurrent fistula over 4 years. All patients had failed standard surgical techniques, and sealant was offered as a minimally invasive method. All patients were given bowel preparation, antibiotics along with meticulous excision of granulation tissue. Overall success was achieved in 60 %.

Cintron et al (1999) initially evaluated patients without bowel preparation or antibiotics, using autologous fibrin sealant. Thorough curettage was performed to remove all granulation tissue, and the procedure was not performed in the presence of acute anorectal sepsis. Wounds were examined on follow-up, and the terms "closure" and "diminished drainage" defined healing. The same group (Park et al., 2000) investigated the use of commercial sealant using a similar technique. Of patients who were followed-

up, 17 reported success at a mean follow-up of 6 months, although success was higher in those who had not previously undergone surgery. On longer term follow-up, Cintron et al (2000) concluded that commercial and autologous sealants were equivalent, however late recurrences were seen, even up to a year following successful closure of openings. Tocchi et al (2000) used commercial sealant and reported that patients with low internal openings were more likely to heal than those with high openings. Patrli et al (2000) reported longer tracks as having a higher chance of success, after he applied a commercial sealant and antibiotic mixture following thorough track curettage and cleansing for several days preoperatively. Such variation in results of fibrin sealant treatment may relate to different track preparations or failure to eradicate secondary tracks prior to sealant instillation. Further work is described in this area, both below and in Chapter 11, for what is essentially, a very simple treatment.

Efficacy Of Fibrin Sealant In The Management Of Complex Anal Fistula: A Prospective Trial

Introduction

Fibrin sealant application to fistula-in-ano offers an attractive alternative, particularly where tracks are complex and fistulotomy might not ordinarily be considered. However, enthusiasm because of short-term success rates of 70-74 percent following sealant treatment (Cintron et al., 1999; Patrj et al., 2000) has been tempered by delayed fistula recurrence (Cintron et al., 2000) which has even occurred after skin healing (Aitola, Hiltunen, & Matikainen, 1999a).

However, it is possible that associated secondary extensions remain unfilled after sealant instillation and may be the cause of recurrence. MRI (Buchanan et al., 2002; Lindsey et al., 2002) accurately depicts both primary tracks and secondary extensions and could thus play an important role, by excluding those patients in whom a complex track system raises the possibility of failure following sealant instillation. This prospective trial used clinical assessment and MRI both in case selection and to predict the outcome of fibrin sealant treatment for patients with complex idiopathic anorectal fistulas considered unsuitable for fistulotomy.

Patients and Methods

Consecutive patients with idiopathic anorectal fistulas were recruited prospectively. Approval for the use of Tisseel TM Kit (two component fibrin sealant)(Baxter AG, Vienna, Austria) had been obtained from the Medicines Control Agency. All patients, in

whom it was preferable to avoid fistulotomy, particularly if fistulas were treated by loose-seton, were eligible. Patients with clinical signs of persisting sepsis, immunodeficiency, Crohn's fistula, hypersensitivity, aged under 18 or females who were currently or considering becoming pregnant were excluded.

MR Imaging

All eligible patients underwent preoperative MRI using a validated protocol (chapter 3). MRI was performed using either a 1.0-T super conducting static magnet (Gyrosan T10-NTTM, Philips Medical Systems, Reigate, UK) or a 1.5-T static magnet (Horizon Echospeed, General Electric Medical Systems, Milwaukee, Wisconsin, USA). Scan findings were reported by the supervising radiologist. Where preoperative MRI depicted secondary extensions (abscesses or horseshoe tracks), patients were excluded prior to surgery.

Examination under anaesthetic

All patients were examined under general anaesthetic by experienced surgeons. No specific bowel preparation was employed. Parenteral antibiotics were administered to all patients at induction (Cefuroxime 1.5g, Metronidazole 500mg). Clinical examination was performed as per usual practice, aided by Lockhart-Mummery and lacrimal fistula probes to help define internal and external openings, if necessary by placing an Eisenhammer retractor within the anal lumen. Once the fistula had been delineated, any indwelling setons were then removed and the primary track was thoroughly curetted using a Volkmann's spoon to remove all granulation tissue. If the track was narrow,

curettage was undertaken using a thin gauze strip or braided suture material. Fistulas were then cleansed using hydrogen peroxide 1.5% and normal saline 0.9% mixed in equal parts in a 20ml syringe via an 51mm 14F gauge single lumen catheter (Abbocath® -T, Venisystems™, Abbott Ireland, Sligo, Republic of Ireland) inserted from the external to the internal opening. This apparatus was substituted for a second single lumen catheter and syringe containing normal saline 0.9 percent to irrigate the track prior to sealant instillation. If catheters could not easily negotiate the fistula lumen, they were deployed using a Seldinger technique via a new number 1 nylon seton. If pus or persisting extensions were found, sealant treatment was abandoned and further surgery was undertaken as deemed appropriate.

Following mechanical and chemical fistula cleansing patients underwent Tisseel™ insertion via the second single lumen catheter. This commercially available fibrin sealant had been prepared in the operating suite. Individual components were mixed and warmed in a Fibrinotherm™ (Baxter AG, Vienna, Austria)(Fig 51), and were then drawn up into two syringes (syringe 1: fibrinogen, factor XIII, fibronectin, aprotinin and plasminogen; syringe 2: thrombin and calcium chloride solution) which were subsequently placed in a Duploject™ (Baxter AG, Vienna, Austria) two-syringe clip where they share a common plunger (Fig 52). A plastic double lumen Y-connector joined these two syringes. This apparatus was then attached to the single lumen catheter (Fig 53), whose tip was visualized at the internal opening. On injection, the components mix at the tip of the catheter to form fibrin sealant. Slow withdrawal of the catheter during instillation, and visualization of sealant protruding from both internal and external openings (Fig 54), ensured track filling. The sealant was set within three

minutes, and no dressings were required. Fistula classification was based on surgical and MRI assessments.



Figure 51: Fibrinotherm used to warm and mix sealant

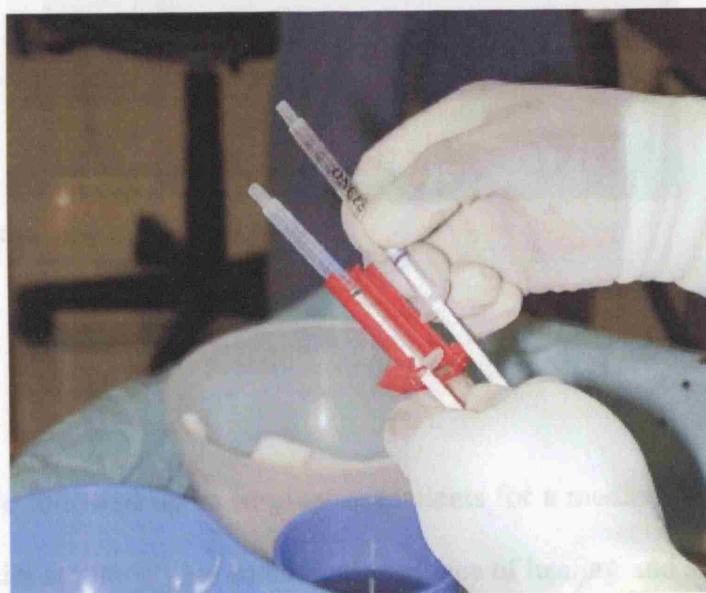


Figure 52: Clip used to hold sealant component syringes



Figure 53: Sealant injected into fistula track



Figure 54: Sealant filling fistula track

Follow up

All patients were followed up in surgical outpatients for a median of 14 months (range 2-24), with special attention paid to clinical evidence of healing and signs of recurrence. Recurrence was defined as discharge, pain, visualization or palpation of either the internal or external fistulous opening. Healing was defined as absence of these symptoms, with both the internal and external openings healed. If at any stage recurrence was denoted, then patients were offered further surgery as deemed

appropriate on clinical grounds, with investigators documenting any subsequent procedures. If healing was detected at the initial outpatient assessment performed at a median of 14 days (range 10-95) postoperatively, then postoperative MRI and further examination were scheduled.

STIR sequence MRI was performed as previously described at a median of three months (range 0.5-9) postoperatively to see whether an underlying fistula remained in those patients with skin healing. Radiologists reported fistulas as either present or absent. In addition, dynamic contrast enhanced MRI (DCEMRI) (Spencer et al., 1996) was also employed in the latter part of the study where tracks had been identified using STIR imaging. T1-weighted contiguous coronal slices were acquired through the anal canal, with patients positioned supine. Scans were taken immediately before and 10, 30, and 50 sec following intravenous gadolinium injection (0.1mmol/kg, Gadoteric acid, Dotarem®, Guerbet, Milton Keynes, Buckinghamshire, UK), using the following scan parameters TR/TE, 6.3/2.1; field-of-view 325 mm; 256 x 256 matrix; 4.25mm slice thickness; no interslice gap; 4 excitations. The supervising radiologist reported whether signal intensity in the fistula remained unchanged or increased following gadolinium injection, based upon review of the laser images and measurement of image intensity using the software tools. Tracks associated with a signal increase on DCEMRI (Fig 54) were defined as active fistulas and predicted recurrence, while tracks with unchanged signal intensity were classified as inactive, representing healing.

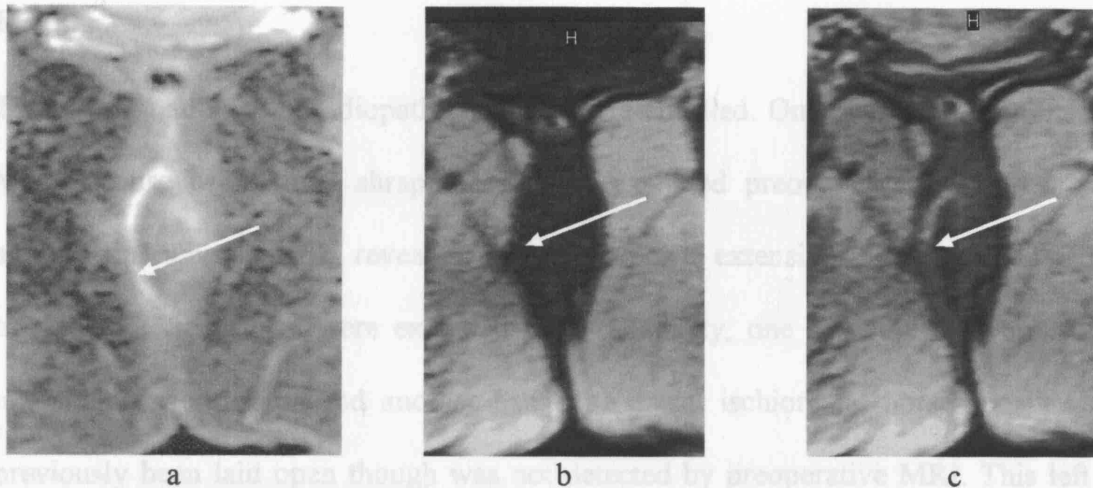


Figure 55: DCEMRI post sealant

Coronal STIR sequence MRI showing a transsphincteric track (arrow) persisting after sealant application (a). The low signal intensity (arrow) on T1 weighted MRI (b), increases after contrast enhancement (c) suggesting persisting inflammation (te arrowhead)

Statistical Analyses

The success of fibrin sealant treatment was determined by the proportion of patients that remained healed at the end of the study period. Clinical and MRI healing rates were compared with time elapsed since surgery. The accuracy, sensitivity, specificity, positive and negative predictive values of clinical examination, STIR sequence MRI and STIR sequence MRI in combination with DCEMRI in predicting outcome after initial skin healing were calculated. The accuracy of these assessments in predicting recurrence was subsequently compared using the Chi squared test. Analysis was performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, Cambridge, UK). Statistical significance was assigned at the 5% level.

Results

Twenty-six patients with idiopathic fistulas were enrolled. One man could not undergo MRI because of retained shrapnel and was excluded preoperatively, together with another in whom MRI revealed an ischiorectal extension. Two patients with transsphincteric fistulas were excluded intraoperatively, one of whom had a purulent intersphincteric abscess and another had a persistent ischiorectal horseshoe that had previously been laid open though was not detected by preoperative MRI. This left 22 patients who underwent sealant instillation (11 men, median age 44 years (range 30 to 65)).

Of the 22 patients, 19 (86.5 percent) had transsphincteric, 1 (4.5 percent) suprasphincteric, 1 (4.5 percent) extrasphincteric and 1 (4.5 percent) rectovaginal fistulas. None had clinical or radiological evidence of secondary extension. Indications for sealant treatment included existing faecal incontinence in 7 patients (32 percent), fear of developing incontinence in 6 patients (27 percent), an anterior transsphincteric fistula in 4 females (18 percent), 3 patients (14 percent) who could not tolerate setons but did not want fistulotomy and 2 patients (9 percent) where either coloanal sleeve anastomosis or martius flap had failed (Table 19, page 223).

Six (27 percent) subjects previously underwent seton placement during primary fistula surgery while 15 (68 percent) had long-term setons for recurrent fistulas (median 3 operations (range 2-15)). One patient (5 percent) with an extrasphincteric fistula had no seton as there was no associated external opening. Setons had been in-situ for a median of four months (range 1-24); in two patients loose setons fell out prior to sealant

treatment. Median operative time was 16 minutes (range 11-25), with a median of 3 ml (range 0.8–10) of sealant required to ensure track filling.

Table 19: Indication for Sealant, Fistula Classification and Level of Internal Opening, Outcome, Further Treatment if Failed, and Follow-up

| Patient | Sex | Indication for sealant | Primary track | Internal opening level | Outcome | Treatment if failed | Follow up (months) |
|---------|-----|------------------------|------------------|------------------------|----------|----------------------|--------------------|
| 1 | F | Martius graft failed | Rectovaginal | Rectal | Recurred | Loose seton | 13 |
| 2 | M | Already incontinent | Transsphincteric | at dentate | Recurred | Loose seton | 18 |
| 3 | F | Anterior fistula | Transsphincteric | at dentate | Recurred | Nil | 2 |
| 4 | F | Already incontinent | Transsphincteric | at dentate | Recurred | Loose seton | 5 |
| 5 | M | Does not like seton | Transsphincteric | at dentate | Recurred | Loose seton | 16 |
| 6 | F | Anterior fistula | Transsphincteric | at dentate | Recurred | Fistulotomy | 14 |
| 7 | F | Fear of incontinence | Transsphincteric | at dentate | Healed | Healed | 14 |
| 8 | M | Already incontinent | Transsphincteric | at dentate | Recurred | Loose seton | 12 |
| 9 | M | Already incontinent | Transsphincteric | above dentate | Recurred | Advancement flap | 16 |
| 10 | F | Does not like seton | Transsphincteric | at dentate | Recurred | Loose seton | 18 |
| 11 | M | Fear of incontinence | Transsphincteric | at dentate | Recurred | Loose seton | 3 |
| 12 | F | Anterior fistula | Suprasphincteric | above dentate | Recurred | Loose seton | 24 |
| 13 | F | Already incontinent | Transsphincteric | at dentate | Recurred | Advancement flap | 15 |
| 14 | M | Fear of incontinence | Transsphincteric | above dentate | Recurred | Loose seton | 20 |
| 15 | M | Does not like seton | Transsphincteric | at dentate | Healed | Healed | 15 |
| 16 | F | Anterior fistula | Transsphincteric | at dentate | Recurred | Nil | 3 |
| 17 | M | Coloanal sleeve failed | Extrasphincteric | Rectal | Recurred | Awaiting proctectomy | 3 |
| 18 | M | Fear of incontinence | Transsphincteric | at dentate | Recurred | Loose seton | 10 |
| 19 | M | Fear of incontinence | Transsphincteric | at dentate | Recurred | Loose seton | 10 |
| 20 | F | Fear of incontinence | Transsphincteric | at dentate | Recurred | Loose seton | 11 |
| 21 | M | Already incontinent | Transsphincteric | above dentate | Recurred | Loose seton | 7 |
| 22 | F | Already incontinent | Transsphincteric | above dentate | Healed | Healed | 15 |

Table 20: Accuracy of Clinical Examination, STIR Sequence MRI and Combined STIR Sequence and DCEMRI for Predicting Fistula Recurrence

| Assessment | Sensitivity | Specificity | PPV | NPV | Accuracy |
|--------------------------|----------------|--------------|---------------|--------------|-----------------|
| Clinical examination | 64 (9/14) | 100 (3/3) | 100 (9/9) | 38 (3/8) | 71 (12/17)* |
| STIR sequence MRI | 100 (14/14) | 67 (2/3) | 93 (14/15) | 100 (2/2) | 94 (16/17)* |
| STIR sequence and DCEMRI | 100 (9/9) | 100 (1/1) | 100 (9/9) | 100 (1/1) | 100 (10/10)* |

Note - numbers are %, NPV = negative predictive value, PPV= positive predictive value.

*p=0.02

Clinical Outcome

Despite skin healing in 17 out of 22 (77 percent) cases at a median of 14 days after treatment, only 3 (14 percent) remained healed at 16 months (Fig. 55). These 3 patients had remained asymptomatic at a minimum of 14 months following treatment (Table 19). In the 19 (86 percent) patients who relapsed, fistula classification remained unchanged, without evidence of abscess or extension formation. Only one patient who recurred underwent fistulotomy for a low transsphincteric fistula, with most others undergoing further sphincter conserving treatments, two declining treatment altogether (Table 19, page 223).

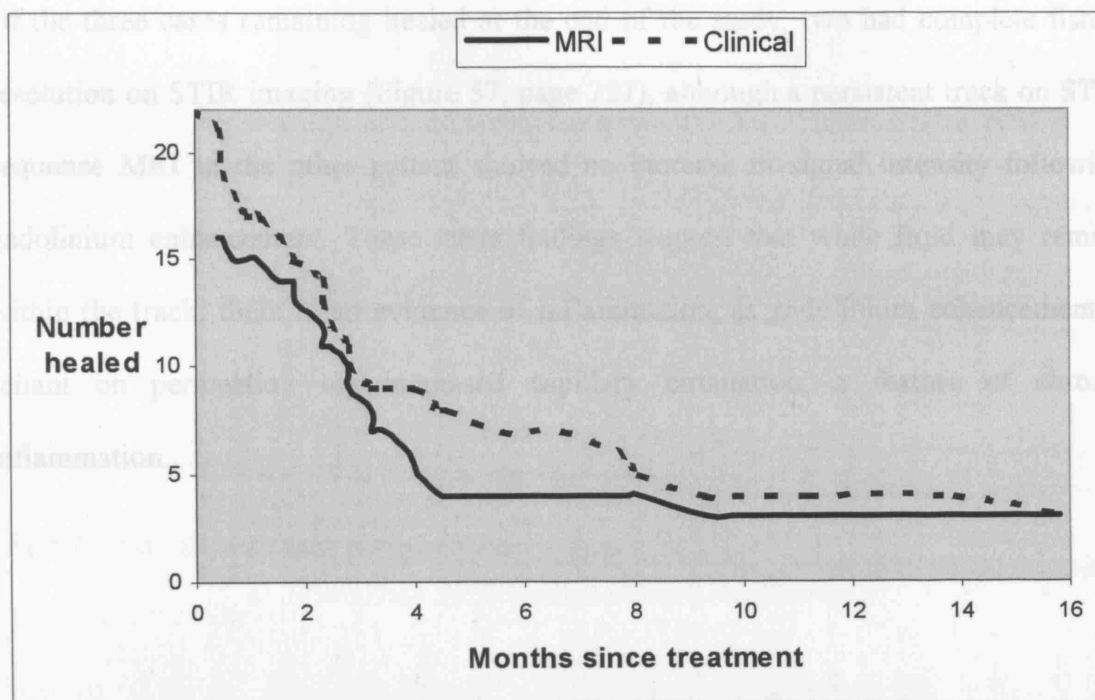


Figure 56: Healing following fibrin sealant treatment for anorectal fistula in 22 patients: clinical and MRI findings

Accuracy of Assessments

Seventeen patients underwent clinical and MRI evaluations when there had been early signs of skin healing. Clinical evaluation was specific with a high positive predictive value, although it lacked sensitivity by failing to predict recurrence in 5 assessments where openings temporarily healed, hence its overall accuracy of 71 percent. STIR sequence MRI was only incorrect once because of a false positive prediction of recurrence where a track was visualized and the fistula did not subsequently recur. A combination of DCEMRI and STIR sequence MRI was used in 10 out of 17 cases and predicted outcome more effectively in all 10 (100 percent) assessments than either STIR sequence MRI alone in 16 out of 17 (94 percent), or clinical examination in 12 out of 17 (71 percent) ($p=0.02$) (Table 20, page 224).

Of the three cases remaining healed at the end of the study, two had complete fistula resolution on STIR imaging (Figure 57, page 227), although a persistent track on STIR sequence MRI in the other patient showed no increase in signal intensity following gadolinium enhancement. These latter findings suggest that while fluid may remain within the track, there is no evidence of inflammation, as gadolinium enhancement is reliant on permeation via increased capillary circulation, a feature of chronic inflammation.

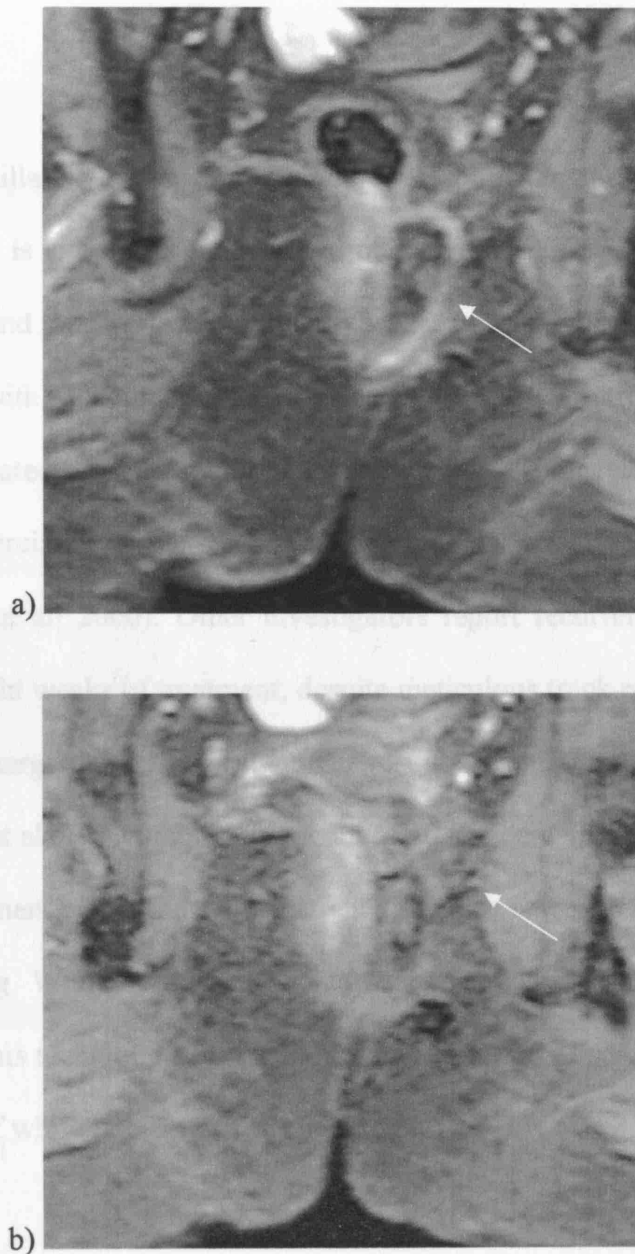


Figure 57: STIR Coronal MRI before and after sealant instillation

MRI of a complex transsphincteric fistula (white arrow) prior to sealant instillation (a), which completely resolves (white arrow) several months after treatment (b).

Discussion

Fibrin sealant instillation has been proposed as a sphincter conserving treatment for fistula-in-ano as it is simple to perform and obviates the need for both inpatient stay, dressing changes and long periods of convalescence. Impressive short-term results using autologous glue, with 81 percent success after one injection (Cintron et al., 1999), have not been substantiated on longer follow-up, with only 54 percent remaining healed at one year. Commercially derived products are equally effective, though simpler to prepare (Cintron et al. 2000). Other investigators report recurrence in 50 percent of patients within eight weeks of treatment, despite meticulous track preparation (Hjortrup, Moesgaard, & Kjaergard, 1991), with similar results treating complex fistulas (Abel et al., 1993). Aitola et al (1999a) noted that 9 out of 10 (90 percent) patients had recurred a month after treatment, with the tenth patient having recurred by six months despite initial skin healing. While fibrin sealant may seem attractive, existing studies do not address whether this technique ever results in the resolution of sepsis, or just temporary symptomatic relief while tracks remains blocked.

In the present study, patients with complex idiopathic primary tracks in whom surgeons would not ordinarily perform fistulotomy were treated. Many were incontinent following previous surgery, some consigned to long-term seton drainage. We excluded those with extensions, as we believed pockets of unobliterated sepsis could be detrimentally sealed in by sealant (Cintron et al., 2000). We also believed that setons promote fibrosis (Parks & Stitz, 1976), and that on seton removal following adequate curettage (Thomson & Ross, 1989) the addition of fibrin sealant might achieve high success rates.

We used TisseelTM (Baxter AG, Vienna, Austria), a sealant that has been employed by previous investigators (Cintron et al., 2000; Park et al., 2000; Patrlj et al., 2000), also using techniques previously described. However, success rates in our study are much lower than those of many series, and are more in keeping with findings of Aitola et al (1999a). Where sealant failed surgeons were reluctant to perform fistulotomy in all but one case (Table 19, page 223), justifying these to be complex primary tracks.

We concur that fistulas may relapse after sealant treatment despite initial apparent healing (Cintron et al., 2000). However, a fistula has only healed when all openings and tracks have been eradicated. This is simple to determine following fistulotomy as the track, once laid open, can be visualized granulating from its base by secondary intention, however uncertainty may remain following a sphincter-conserving technique.

Fibrin sealant has recently been shown to be more successful for complex fistulas than conventional treatment (Lindsey et al., 2002), and is associated with a higher degree of patient satisfaction. However, this and other studies assessing sphincter-preserving treatments for anal fistula, including surgical advancement flap or the use of Infliximab, have used skin healing as a surrogate for fistula healing. This study employed MRI as a noninvasive tool to monitor fistula healing beneath the skin, as MRI better predicts the outcome of fistula surgery than EUA findings (Spencer et al., 1998). A previous study using MRI following sealant application to a group of mainly simple fistulas (Chan et al., 2002) did not find imaging useful, however, scans were undertaken quite early in the postoperative period, where it may be difficult to differentiate haemorrhage from underlying sepsis (Spencer et al., 1996). Although we encountered one error using STIR

sequence imaging in the present study, this technique used alone, or in combination with DCEMRI was superior to clinical assessment in predicting outcome.

While all assessments showed a high positive predictive value for determining recurrence, MRI could predict recurrence well in advance of the clinical setting. Indeed, at four months MRI could predict outcome for the rest of the study in all but one patient, who had defaulted their initial scan appointment. While this did not alter clinical management, it has importance in defining outcome of this minimally invasive technique. This present study has also shown, for the first time, that a small minority (14 percent) of complex anorectal fistulas can actually be cured using fibrin sealant when considering combined clinical and radiological evidence.

Although fistulas may be adequately cleansed prior to sealant instillation, curettage is unlikely to remove all granulation tissue, the hallmark of chronic inflammation. Fibrin sealant acts initially as a tissue matrix, allowing cellular influx and collagen formation. At least half of its volume is reabsorbed in less than two weeks. Whilst this may be part of the reason for early failure of the technique, it is likely that poor track preparation fails to provide the correct environment for this process to take place. In addition, as fistula-in-ano are often epithelialised (Lunniss et al., 1995b), failure to adequately curette out all of this tissue may further jeopardise the likelihood of success. Adequate fistula preparation might only be achieved using techniques like core out, or laser, fistulectomy (Salim & Ahmed, 2001) and further work is required in this area.

Sentovich (2003) recently reported on 48 patients treated by internal gland destruction and drainage seton for two months prior to fibrin sealant. The internal opening was

closed with a single suture. After retreatments 33 patients showed clinical closure of their tracks at a median follow-up of 22 months. Zmora *et al.* (2003), who retrospectively assessed patients with cryptoglandular fistula receiving fibrin sealant, noted that at a mean follow-up of 12 months, the healing rate was higher when sealant was performed in conjunction with an endorectal advancement flap (54%) compared to sealant alone (33%). These recent reports suggest that sealant instillation alone is likely to be inadequate.

New techniques are often integrated into existing practice before a full appreciation of their value. It has been suggested that fibrin sealant treatment could be used in all fistulas (Sentovich, 2001), however this present study shows that short-term results are misleading. Fistula healing following sealant application can only be determined by adequate follow-up, with consideration of underlying track activity, not just skin healing, incorporated in the definition.

Despite these seemingly disappointing medium term results, it must be emphasized that fibrin sealant treatment for fistula-in-ano is simple. Indeed, no patient who relapsed in this study developed new abscesses. As such, for patients with complex primary tracks where surgeons might ordinarily precipitate incontinence by fistulotomy, or where patients are already incontinent, this technique could be offered as a benign, though less successful, alternative.

In conclusion, the success of fibrin sealant application for complex anorectal fistulas, without extension, is 14 percent in the medium term, which must be considered when

advising treatment. MRI findings predate the clinical scenario, and can, thus, accurately predict outcome in those with skin healing.

Chapter 11

Pilot Study: Fibrin Sealant in Experimental Model of Anal Fistula

Introduction

Failure following fibrin sealant therapy for complex fistula-in-ano is not due to persistent extensions (chapter 10) and probably relates to inadequate track preparation. Persistence of fistula-in-ano was initially thought related to chronic infection of fistula tracks and intersphincteric glands (Parks & Morson, 1962), however, with few pathological organisms actually detectable in fistulas (Lunniss et al., 1993; Seow-Choen et al., 1992), Lunniss and co-workers (1995b) postulated that track epithelialization and granulation tissue lining the tracks led to their chronicity. Track preparation prior to sealant instillation has, until now, consisted of curettage of this lining, as it has been assumed that sealant is more likely to provide a viable matrix allowing fibroblast adherence and healing in the presence of fibrous versus granulation tissue. Similarly, loose-seton treatment following meticulous fistula curettage permits fibrosis and healing on subsequent seton removal in up to 40% of patients (Thomson & Ross, 1989) this method might optimally prepare tracks for fibrin sealant treatment.

Although anal MRI (Lunniss et al., 1992) provides a non-invasive method of monitoring the underlying success of sphincter conserving treatments (chapter 10) (Bell et al., 2003a) comparison with fistula histology has been unfeasible and no experimental data on anal fistula healing using fibrin sealant are available. This prospective study had two aims. Firstly, to create an experimental porcine model of fistula-in-ano and, secondly, using this model, to assess fistula track preparation, the use of setons and the effects of sealant instillation on the prepared track in order to optimize track preparation prior to fibrin sealant treatment.

Methods

Personal and project licences were granted by the Home Office, fulfilling the requirements of the 1986 Animal Procedures Act. Male Large White/ Landrace crossbred pigs were used, as the arrangement of their external anal sphincter (EAS) encircling the anal canal is more in keeping with humans than female pigs (O'Bichere et al., 2000a).

Initial cadaveric dissection enabled refinement of the technique for fistula formation and noted a rudimentary IAS. The intersphincteric plane was hard to visualize macroscopically, although this component, together with structures resembling anal glands could be viewed microscopically (figure 58 a & b, page 236), which also confirmed the poorly developed IAS smooth musculature.

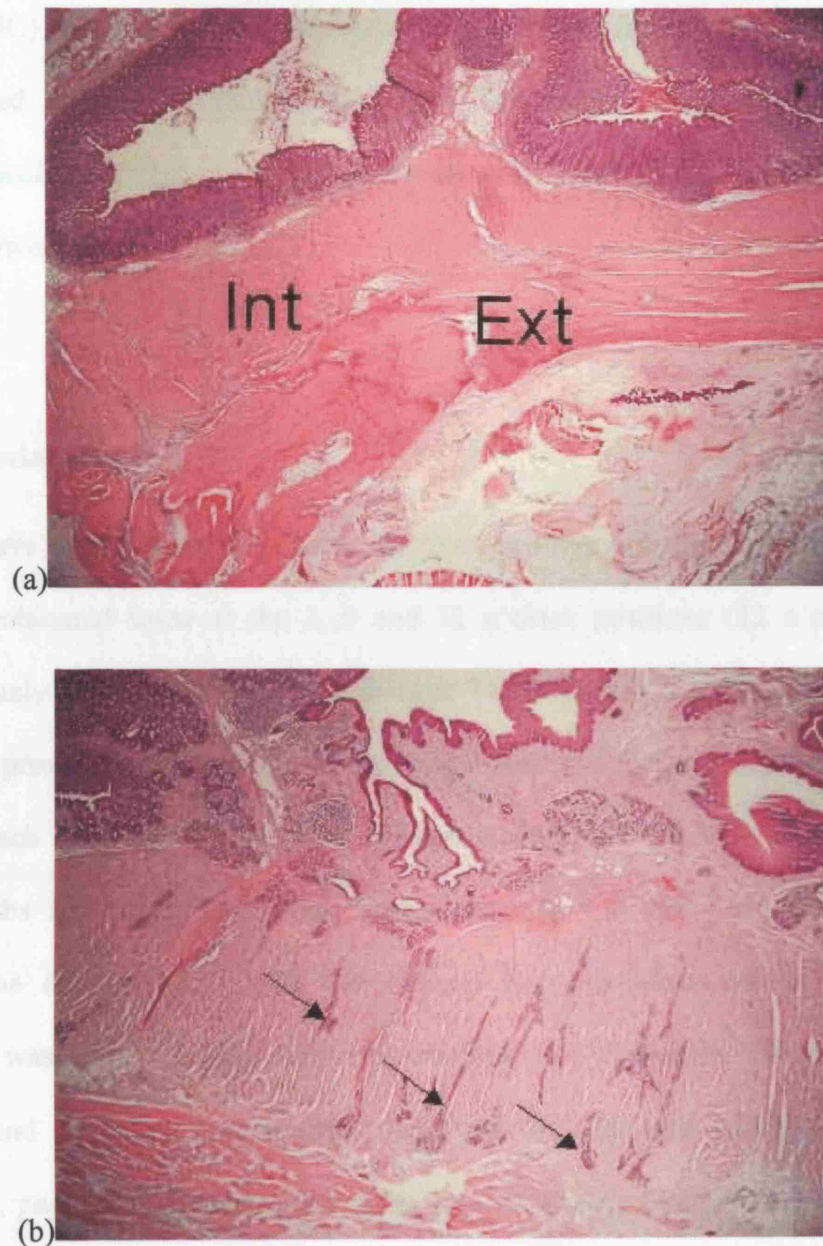


Figure 58: Histology of porcine anal canal

(a) Histological appearances of porcine anal canal musculature, showing an internal anal sphincter (Int) and external (Ext) sphincter.

(b) Intramuscular anal glands (arrowed) are laterally placed in the internal sphincter.

Following these preliminary studies, eight adult male pigs (38-41 kg) underwent surgical fistula creation following premedication (Ketamine 5mg/kg (Pharmacia) and Xylazine 1mg/kg (Bayer)) given approximately one hour before standard general

inhalational anaesthetic (4-5% halothane (Zeneca) in 4 litres oxygen and 1 litre nitrous oxide (BOC) per minute), administered by a close fitting mask. Each pig was administered Ampicillin (Intervet) IM 5mls, Ivermectin (MSD Aguet) s/c 1ml and 3.2ml Carprofen (Pfizer) s/c analgesia as well as Iron and B12 to prevent anaemia in a rapidly growing animal.

Fistula Model Creation

All pigs were examined supine in the lithotomy position. Minimal incisions were made into the ischioanal fossa at the 3, 9 and 12 o'clock positions (12 o'clock anterior) approximately 2cm lateral to the anal margin. The 6 o'clock position was not employed due to its proximity to the tail and concerns about precipitating sepsis via the spinal cord. In each of these sites, a 14 F Abocath catheter (T 14 G 51 mm Venisystems, Abbott Labs Ltd, Kent UK) was directed through the anal sphincter musculature towards the dentate line. Once the catheter had punctured the anal mucosa, its introducer was removed and a seton was introduced via its lumen. The sheath was then removed and the seton was loosely tied encircling the anal sphincter musculature (Figure 59, page 238). Either silastic tube, non-absorbable braided polyester (Ethibond no. 1- Ethicon (Johnson and Johnson Intl)) or nylon (Ethilon no. 1 – Ethicon (Johnson and Johnson Intl)) setons were used in each fistula, according to table 1. Immediately after this and subsequent procedures animals were recommenced on their standard diet, and received temgesic as analgesia for the first 48hrs. Animals were monitored daily, particularly for signs of undue distress or severe perianal sepsis.

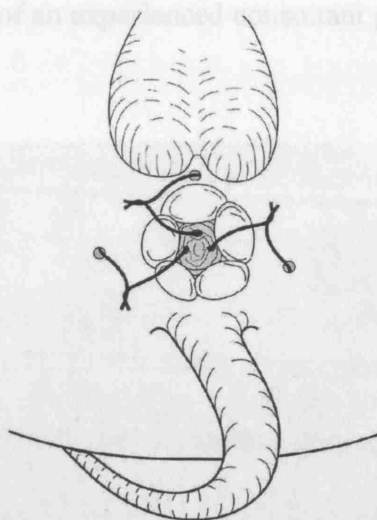


Figure 59: Placement of setons in porcine model

Setons and fistula were placed at 3, 9 and 12 o'clock (Anterior is 12 o'clock).

At this point, animals were randomly assigned to undergo stereological histological assessment of fistulas (n=2) (control group), fistula curettage with delayed killing and histological assessment (n=2) (seton group) or fistula curettage, fibrin sealant treatment with delayed killing and histological assessment (n=4) (sealant group) according to the schedule in table 20. Setons (nylon, silastic and ethibond) were equally distributed (p=1) across these groups.

After 26 days all 8 pigs were similarly re-anaesthetised and underwent fistula MRI, EUA and seton removal, together with microbiological assessment.

MR Imaging

Body coil MRI was undertaken before EUA using a 1.5-Tesla super-conducting magnet (Philips Medical Systems, London, UK) in a specialised mobile veterinary MRI unit

(Figure 60, 239) with its own animal anaesthetic circuit. Animals were scanned supine under the direct supervision of an experienced consultant gastrointestinal radiologist.



Figure 60: Mobile Veterinary MRI unit

The long axis of the anal canal was identified using a midline sagittal T2 -localising scan and then axial and coronal STIR sequences planned with respect to the anal canal axis using the following scan parameters: TR/TE, 3003/15; field-of-view 300 mm; 3mm slice thickness; 1mm interslice gap. MR Imaging was analysed using a dedicated MR workstation (Easyvision, Philips Medical Systems, Hammersmith, United Kingdom). An experienced blinded observer initially denoted the presence or absence of a fistula on MRI, defined as a track crossing the sphincter complex and accessing the intersphincteric space (Figure 61, page 240). The signal intensity and volume of each fistula detected were measured. All measurements were made using axial images with the imaging window set at: - width 2450, level 1250. Using the workstation based image analysis software, the cross-sectional area of each fistula was measured by tracing its perimeter on the axial image. Areas of individual fistulas appearing on sequential MRI slices were summated (mm^2), and the volume of each fistula was calculated in mm^3 by multiplying this sum by 3.5 (3mm slice thickness, 1mm inter-slice

gap). The mean fistula signal intensity automatically derived from the cross-sectional area analysis was also denoted. Using these values for each slice, the mean signal intensity (I) per unit area of each fistula was calculated (I/mm^2).

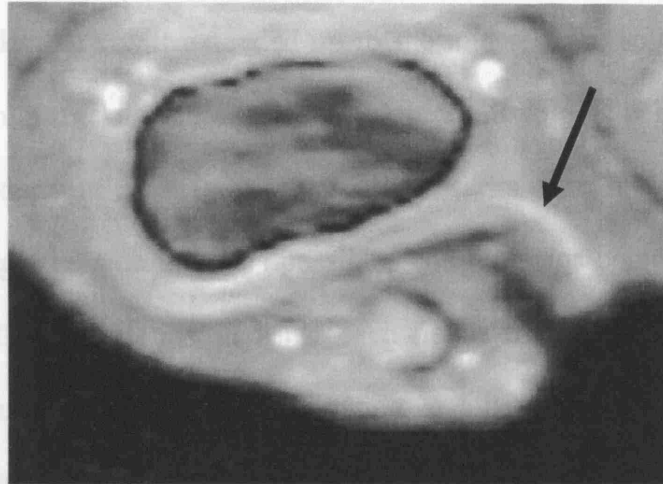


Figure 61: Porcine MRI demonstrating a fistula (arrowed) crossing the porcine anal sphincter.

Examination under anaesthetic and Microbiological Assessments

All animals were re-examined in the operating suite under the same anaesthetic to determine the clinical state of the created fistulas. Setons were removed and microbiology culture swabs obtained from the anal canal, perineum and each fistula track. Fistulas were swabbed from the external rather than the internal opening to prevent contamination from anal canal organisms. Swabs were cultured using blood agar plates and read by Microbiologists, blinded to their site of origin, who stated whether organisms were predominantly faecal or skin derived.

Fistula Management

The two control pigs underwent anorectal excision under terminal anaesthesia, to obtain histology. Commencing posteriorly, a circumanal incision was fashioned using electrocautery (Figure 62, page 241), which included the perineum and a margin lateral to the fistula tracks. This was extended up to the mid rectum, so that the anal canal, perineum and fistula tracks were excised *en bloc*. The two pigs being treated by seton removal alone underwent curettage of their fistula tracks using a Volkmann's spoon to remove as much granulation tissue as possible. The four pigs being treated with fibrin sealant additionally had this instilled into each fistula track according to the protocol described previously (chapter 10). Following fistula curettage and normal saline irrigation, Tisseel® fibrin sealant was prepared and instilled using a catheter inserted into each external fistula opening extending as far as the internal opening. During instillation the apparatus was slowly withdrawn to ensure filling of the whole fistula track, until sealant protruded from both internal and external openings.

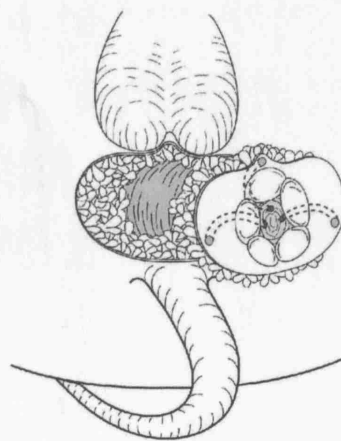


Figure 62: Dissection *en bloc* of porcine anorectum and fistula tracks to obtain histology.

MRI was repeated under terminal anaesthesia in the seton and sealant groups a median of 47.5 days after fistula formation (3 on day 42, 3 on day 53). This was followed by excision of the anorectum to enable stereological histological examination of the tracks, according to the schedule in Table 21 (page 243).

Table 21: Experimental schedule for 8 pigs following fistula creation and seton placement.

| Animal no. | Group | EXPERIMENTAL SCHEDULE | | | | |
|------------|----------------|------------------------|------------|------------------|----------------|-----------|
| | | Fistula site (o'clock) | Seton type | Day | | |
| | | | | 0 | 26 | 42 |
| 1 | Control | 3 | Silastic | Fistulas created | MRI | |
| | | 9 | Nylon | | | |
| | | 12 | Ethibond | | Seton removal | - |
| 2 | | 3 | Ethibond | | Histology | - |
| | | 9 | Silastic | | | |
| | Seton | 12 | Nylon | Setons placed | | |
| 3 | | 3 | Silastic | | MRI | MRI |
| | | 9 | Nylon | | | |
| | | 12 | Ethibond | | Seton removal | Histology |
| 4 | | 3 | Nylon | | Curettage | MRI |
| | Fibrin Sealant | 9 | Ethibond | | | |
| | | 12 | Silastic | | | |
| 5 | | 3 | Nylon | | MRI | MRI |
| | | 9 | Ethibond | | | |
| | | 12 | Silastic | | Histology | - |
| | Fibrin Sealant | 3 | Nylon | Setons placed | | |
| 6 | | 9 | Ethibond | | Seton removal | - |
| | | 12 | Silastic | | | |
| | | 3 | Ethibond | | Curettage | MRI |
| 7 | | 9 | Silastic | | | |
| | Fibrin Sealant | 12 | Nylon | | | |
| | | 3 | Silastic | | | |
| | | 9 | Nylon | | | |
| 8 | | 12 | Ethibond | | Fibrin sealant | MRI |
| | | | | | | |

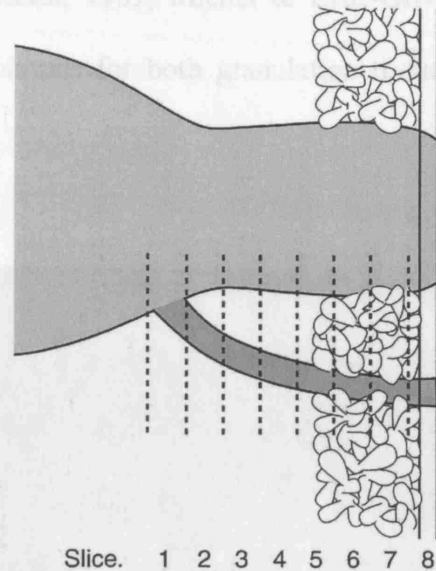


Figure 63: Preparation of fistula cores into equal slices (dashed vertical lines).

Eight sections were obtained and stained with haematoxylin and eosin for microscopic analysis.

Histological Assessment

Resected specimens were placed in 10% neutral buffered formal saline for at least seven days to enable adequate fixation. Specimens were then gross cut longitudinally, providing tissue cores that encompassed each fistula or region that the fistula had been sited along with a circumferential cuff of normal tissue approximately 1cm in diameter. Now in the axial plane, each core was subdivided to provide eight equal slices from each fistula (Figure 63, page 244). Five-micron sections were obtained from each serial fistula slice and stained with haematoxylin and eosin, thus providing microscope slides for analysis. An experienced pathologist, blinded to the method of fistula treatment (control, seton or sealant), assessed on each slide the fistula lumen and granulation

tissue area, according to a grid of quadratic points applied overlying the viewing screen (Figure 64, page 245). Measurements obtained were summated according to Cavalieri's principle (Gundersen & Jensen, 1987; Michel & Cruz-Orive, 1988), thereby providing stereologically acquired volumes for both granulation tissue and fistula lumen in each fistula.

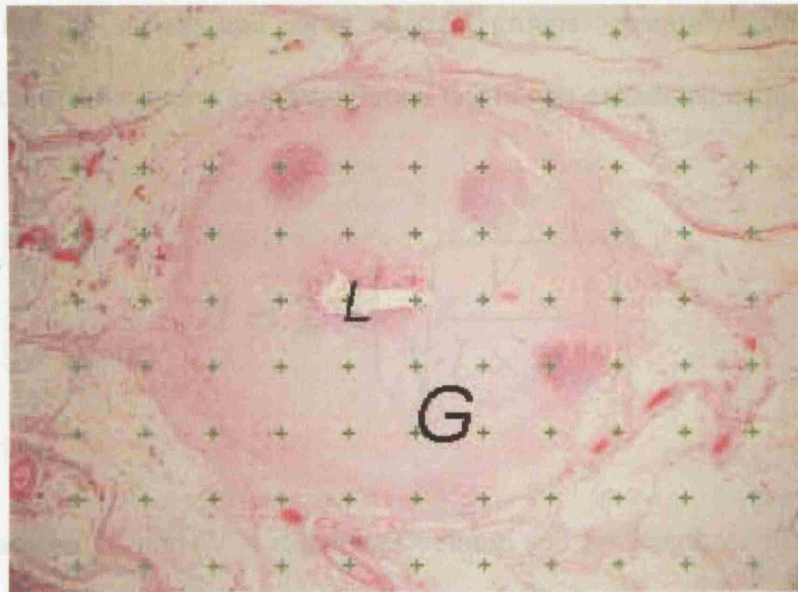


Figure 64: Stereological assessment of fistula.

A grid of quadratic points overlying the viewing screen enabled calculation of fistula lumen (L) and granulation tissue (G) size. This appearance was typical of fistulas in the control group

Statistics and analyses

Microbiological culture swabs were compared for the predominance of skin (staphylococcus, diptheroids), faecal (coliforms, anaerobes, streptococcus faecalis) or indeed absence of organisms, using Fisher's exact test. Histological volumes of granulation tissue and fistula lumen, and the volume of inflammation seen on MRI were compared between control fistulas and those fistulas treated using fibrin sealant or loose

setons. The Kruskal-Wallis and Mann-Whitney tests were used to compare non-parametric continuous data. The strength of the association between volumes obtained using MRI and the three histological volume measures (fistula lumen, granulation tissue, fistula lumen and granulation tissue combined) were examined using the Spearman's Rank correlation coefficient for non-parametric data. Fistula intensity on MRI was compared between groups using ANOVA, and was compared between days of termination for the sealant and seton removal groups separately using t-tests. The diameter of the fistula lumen and granulation tissue was calculated using the following formula:

$$d = 2 \times \left(\sqrt{\frac{V}{L \times \pi}} \right)$$

where, d =diameter in mm, V = calculated volume and L = length of fistula, assuming that these components were cylindrical in shape and of uniform thickness along their length. Analysis was performed using Arcus Quickstat Biomedical (Version 1.2, Research Solutions, Cambridge, UK) and Stata (Version 7, Stata Corporation, Texas, USA). Statistical significance was assigned at the 5% level.

Table 22: Comparison of predominant organisms cultured from anal canal, fistula lumen and perineum in 8 pigs

| | Perineum (n=8) | Fistula Lumen (n=8) | Anal canal (n=8) | p |
|--------------------------|-------------------|------------------------|---------------------|--------------|
| Organism cultured | | | | |
| Nil | 1 | 0 | 0 | |
| skin* | 5 | 4 | 0 | 0.002 |
| Faecal+ | 2 | 20 | 8 | |
| Total | 8 | 24** | 8 | |

(**each pig had 3 fistulas)

Skin organisms (staphylococcus, diptheroids)*

Faecal organsims (coliforms, anaerobes, streptococcus faecalis)+

Results

All fistulas were satisfactorily created, with no adverse observations recorded postoperatively. At repeat EUA at 26 days, each pig had three anal fistulas adequately drained by setons, except in one case where a seton had fallen out, although this fistula was still easily probed. One of the fistulas, together with its encircling ethibond seton, had migrated caudally as the seton seemed to have been too tight, whilst all other fistulas remained within the anal canal. Twenty of 24 fistulas cultured faecal organisms. Fistula swabs were more often associated with faecal than skin-derived organisms, when compared to both perineal and anal canal swabs ($p=0.002$) (Table 22, page 247).

Fistula Morphology

Sections fell into three broad groups; those where a fistula lumen and surrounding granulation tissue were present, which was usually in the control group (Figure 64, page

245); those where no lumen was present but granulation tissue was conspicuous and interpreted as being at the site of a healed fistula (Figure 65, page 248). This latter appearance was often associated with neo-vascularisation. In the third group there was no evidence of granulation tissue or a lumen. Epithelialisation was not evident in any track. While no sealant was evident microscopically in any case, occasional sections showed signs of a foreign body type reaction, characterised by a marked chronic inflammatory infiltrate associated with occasional giant cells (Figure 66, page 249).

The granulation tissue present in untreated porcine fistulas was similar to that seen in human fistula-in-ano, when directly compared with granulation tissue obtained from one human with a primary trans-sphincteric fistula (Figure 67, page 249).



Figure 65: Histological appearance where no lumen was present, and granulation tissue was interpreted as being at the site of a healed fistula

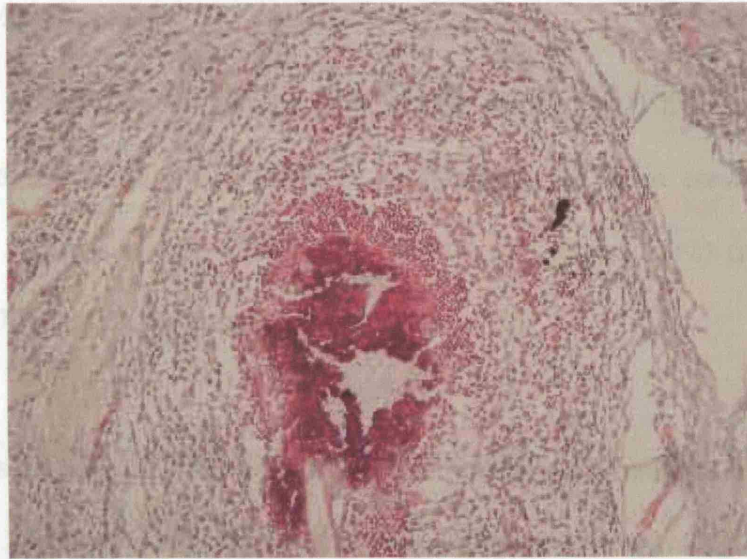


Figure 66: Foreign body reaction after sealant

Histological appearance of a track post sealant where a foreign body reaction, characterised by a marked chronic inflammatory infiltrate associated with occasional giant cells.

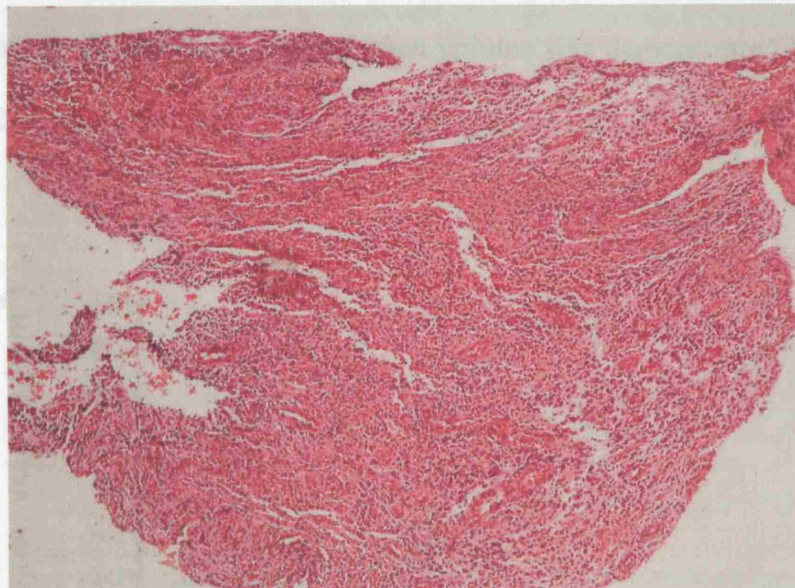


Figure 67: Human fistula histology

Histological appearance of a human fistula-in-ano was very similar to the granulation tissue present in untreated porcine fistulas (see fig 64).

Histological Measurements

In the control group, fistulas treated with silastic setons (n=2) had smaller diameters (median 3.73mm (range 3.62-3.84)), in comparison to those treated using nylon (n=2)(median 5.25mm (range 3.39-7.11)) or ethibond setons (n=2) (median 5.45mm (range 5.13-5.76)), although numbers were small.

Granulation tissue volume was least in sealant (median 88 mm³ (range 36-341)) and seton (median 187 mm³ (range 87-485)) groups, compared to controls (median 453 mm³ (range 201-1304))(p=0.002). Fistula lumen volumes (p<0.001) (Figure 68, page 250) and volumes of granulation tissue and fistula lumen combined (p=0.002) were similarly smaller (see table 23, page 253)(Figure 69, page 251). Furthermore, while granulation tissue volume decreased significantly between days 42 and 53 in both those seton and sealant groups, no difference in fistula lumen volume was demonstrated between these times (table 23, page 253).

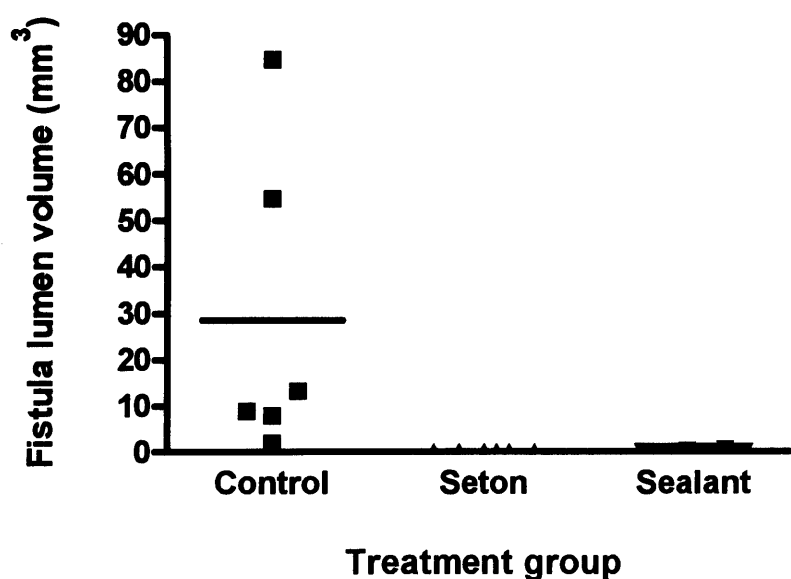


Figure 68: Histological measurement of fistula lumen volume in control, seton and sealant groups.

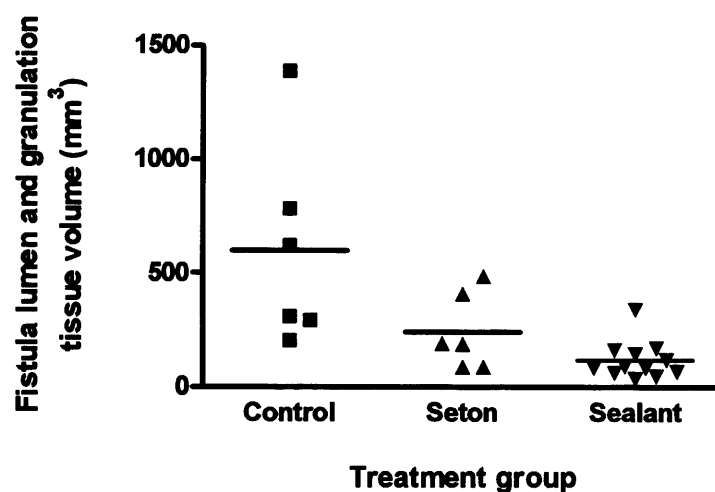


Figure 69: Histological measurement of combined fistula lumen and granulation tissue volumes in control, seton and sealant groups.

The combined diameter of the fistula lumen and granulation tissue ranged between 1.24-7.11 mm. Overall, this diameter was greatest in the control fistulas (median 4.49mm (range 3.39-7.11)), compared to seton (median 2.91mm (range 1.67-4.32)) or sealant groups (median 1.9mm (range 1.24-4.25))(p=0.004).

MRI Measurements

Magnetic resonance imaging fistula volume measurements were smaller in sealant (median 29.93mm³ (range 0-269.5)) and seton groups (median 26.25mm³ (range 0-158.2)) versus controls (median 131.95mm³ (range 0-1433.6))(p=0.024) (fig 69). However, there was no difference between seton or sealant groups (p=0.89). Whilst these volumes diminished over time, differences were only significant for those treated using sealant, reflecting the small sample sizes (table 24, page 254).

Whilst MRI fistula intensity was smallest in the sealant group, in comparison to seton and control fistulas ($p=0.003$)(fig 70)(table 23), there was no difference in the intensity of treated fistulas over time (table 24, page 254).

Histological versus MRI measurements

There was no relationship between volume of fistulas measured using MRI, and histological measurement of fistula lumen volume (R value=-0.11, $p=0.61$), granulation tissue volume ($R =0.40$, $p=0.18$) or fistula lumen and granulation tissue volumes combined ($R =0.16$, $p=0.45$), using the Spearman's correlation coefficient (R).

Table 23: Histological volume of fistula lumen and granulation tissue, and MRI fistula intensity compared between control, seton and sealant groups.

| Groups | Control | Seton | Sealant |
|-------------------------|----------------|--------------|----------------|
| Pigs (number) | 2 | 2 | 4 |
| Fistula tracks (number) | 6 | 6 | 12 |

| Histological volumes (median (range), mm ³) | Control | Seton | Sealant | P |
|---|----------------------|------------------|-------------------|-------------------|
| Fistula lumen (F) | 11.0 (2.0-84.6) | 0 (0) | 0 (0- 0.5) | <0.001* |
| Granulation tissue (G) | 453 (201- 1304) | 187 (87- 485) | 88 (36-341) | 0.002* |
| F + G | 464 (203- 1388.6) | 189 (87- 485) | 88 (36- 341.5) | 0.002* |
| MRI fistula intensity (Mean (s.d.) units/ mm ²) | 1214 (234) | 978 (174) | 777 (200) | 0.003+ |

* Kruskal-Wallis test; + ANOVA.

Table 24: Change in histological fistula lumen and granulation tissue volumes, and MRI determined fistula intensity and volume over time

| Sealant | Day 26 | Day 42 | Day 53 | |
|---|-----------------------|----------------------|----------------|--------|
| Number fistulas | 12 | 6 | 6 | |
| Histological volumes (mm ³) (median (range)) | | | | P |
| Fistula lumen (F) | ~ | 0 (0-0.5) | 0 (0-0.4) | 0.90* |
| Granulation tissue (G) | ~ | 152 (61-341) | 75 (36-90) | 0.03* |
| F + G | ~ | 152 (61-341) | 75 (36-90) | 0.03* |
| MRI volumes (mm ³) (median (range)) | 184.1 (13.7-555.8) | 40.25 (11.9-62.0) | 0 (0-269.5) | 0.02+ |
| MRI fistula intensity ((units/ mm ²) mean (s.d.)) | ~ | 790 (191) | 762 (232) | 0.83** |

| Seton | Day 26 | Day 42 | Day 53 | |
|---|---------------------|-------------------|----------------------|--------|
| Number fistulas | 6 | 3 | 3 | |
| Histological volumes (mm ³) (median (range)) | | | | |
| Fistula lumen (F) | ~ | 0 (0) | 0 (0) | ~ |
| Granulation tissue (G) | ~ | 408 (187-485) | 88 (87-190) | 0.03* |
| F + G | ~ | 408 (187-485) | 88 (87-190) | 0.03* |
| MRI volumes (mm ³) (median (range)) | 399.9 (0-1433.6) | 25.9 (0-111.7) | 26.6 (11.2-158.2) | 0.36+ |
| MRI fistula intensity ((units/ mm ²) mean (s.d.)) | ~ | 886 (110) | 1038 (202) | 0.42** |

* Mann-Whitney test;

** t-test; Kruskal-Wallis test+; ~ values where no measure or analysis

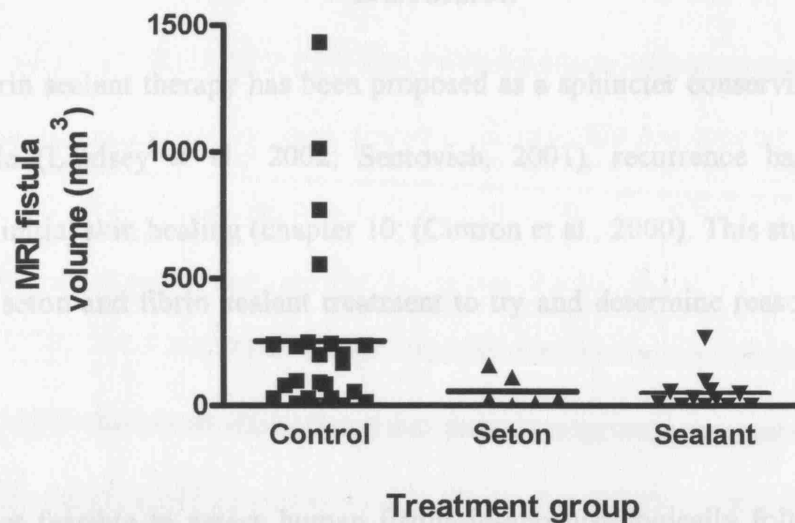


Figure 70: MRI comparison of fistula volumes

Volume of fistulas measured using magnetic resonance imaging (each of the 24 fistulas acted as a control prior to treatment) in control, seton and sealant groups.

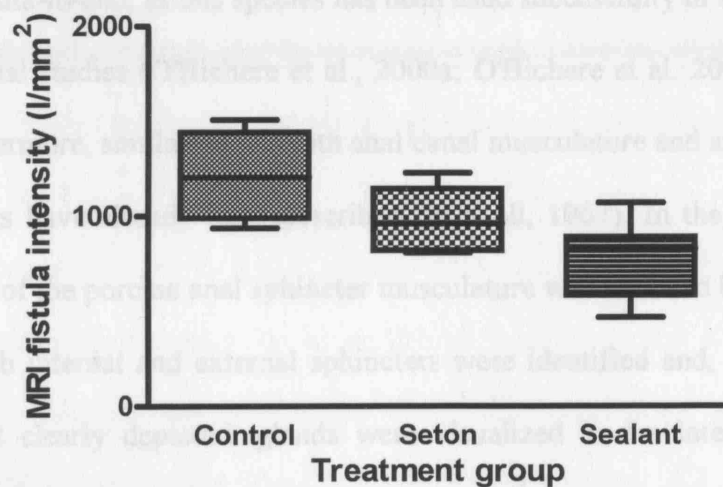


Figure 71: Fistula intensity measured using MRI in control, seton and sealant groups.

Discussion

Whilst fibrin sealant therapy has been proposed as a sphincter conserving treatment for anal fistula (Lindsey et al., 2002; Sentovich, 2001), recurrence has occurred even following initial skin healing (chapter 10; (Cintron et al., 2000). This study explored the effects of seton and fibrin sealant treatment to try and determine reasons for technical failure.

As it is not feasible to assess human fistula-in-ano histologically following sphincter conserving treatments, an experimental animal model was developed for this purpose. The ideal model for fistula-in-ano is the dog (Greiner, 1981; Harvey, 1972), however this species is not acceptable for experimental study. Instead, we developed a porcine model of fistula-in-ano, as this species has been used successfully in several other recent gastrointestinal studies (O'Bichere et al., 2000a; O'Bichere et al. 2000b; Wagner et al. 2000). Furthermore, similarities in both anal canal musculature and anal glands between man and pigs have already been described (McColl, 1967). In the present study, the arrangement of the porcine anal sphincter musculature was found to be similar to that in humans. Both internal and external sphincters were identified and, although a dentate line was not clearly depicted, glands were visualized in the intersphincteric space. Furthermore, fistulas were easy to create, seemed to be well tolerated and were similar to human fistulas when assessed by MR imaging and indeed histologically. The majority of fistulas cultured enteric organisms, as predominate in human fistula-in-ano (Grace, Harper, & Thompson, 1982; Lunniss et al., 1993)

The endpoint of fistula healing is the disappearance of the lumen, with subsequent maturation of granulation tissue into a collagenous scar (Cotran, Kumar, & Collins,

1999). In the present study, the lumen disappeared following treatment with curettage after seton removal, either with or without fibrin sealant. However, the fistulas created experimentally were acute, in comparison to chronic fistulas treated in human series (Cintron et al., 1999; Thomson & Ross, 1989) (chapter 10). Whether these two surgical techniques are equivalent for anal fistula, or that the fistulas in the model might have closed spontaneously, notwithstanding time and intervention, has not been answered in this short study. For a realistic comparison, fistulas may need to be present for a longer duration prior to treatment. Furthermore, Lunniss et al (1995b) postulated chronicity of human fistula-in-ano may relate to track epithelialisation. Whether epithelialisation and chronicity would have occurred in our model given a longer time frame remains unclear.

Previously we had proposed that seton removal and curettage would provide the best chance for cure prior to fibrin sealant treatment. However, complete healing occurred in only 14% of patients with complex tracks (chapter 10). Similarly, disappointing long-term results were realised in those patients who had previously been treated by the loose-seton technique (chapter 9), where delayed seton removal was performed after resolution of sepsis (Kennedy & Zegarra 1990; Thomson & Ross 1989). In the present study, volumes of granulation tissue and MRI fistula intensity were consistently lower in tracks treated by sealant after seton removal and curettage. Furthermore, the volume of granulation tissue fell over time. These experimental results favour sealant over seton treatment.

This present study has demonstrated a larger volume of granulation tissue relative to the fistula lumen volume. It has been suggested that fistula curettage using a Volkmann's

spoon might remove all granulation tissue (Cintron et al., 1999). In this study, granulation tissue volume was highest in the control group, decreasing significantly after curettage and furthermore with sealant. Granulation tissue volume decreased over time, but there was still some present, even 53 days after curettage with or without sealant therapy. It would seem logical that recurrence is due to retained granulation tissue. As the diameter of this may be up to 7mm, core-out fistulectomy (Schouten & van Vroonhoven, 1991) would seem appropriate to ensure complete healing after sealant instillation. Interestingly, Tasci and coworkers (2003) have recently reported favourable results using a new device, the "Fistulectome" which excises the fistula track and approximately 2-mm of tissue circumferentially, thus "coring-out" the fistula.

This report represents the first successful experimental model of fistula-in-ano. McColl (1967) previously tried to create fistulas in dogs, by ligating their anal scent gland outlet ducts, however, in that study no fistulas were found, even following *E Coli* instillation, and the only sign of glandular infection related to an anal intramuscular gland. Following comparative anatomical studies, McColl suggested that canine intramuscular anal glands were more likely to be associated with fistula than their scent glands and concluded that he had directed his experiments towards the wrong glands.

The present study does, however, have several potential sources of error. Due to the need to know fistula histology, control fistulas were sectioned earlier than those treated with sealant or seton removal. It would be interesting to know the outcome of control tracks had these been left with a seton in or, if setons had been removed without curettage. Any future research would need to encompass these assessments.

Stereology proved a useful method for measuring fistula lumen and granulation tissue volume. Cavalieri's Principle (Gundersen & Jensen, 1987), upon which this technique is based, assumes that the objects being measured are cylindrical, however this may not always be the case along the length of a fistula, and indeed this is another potential source of error. Our method of calculating fistula volume using imaging might also be subject to similar errors. Whilst we could clearly see fistulas using MRI, the methods employed provided smaller scale images than in human scans, therefore these measurements may be inaccurate. In addition, the high signal depicted on STIR imaging probably over-represents fistula size as there is already likely to be considerable flare around a fistula, which may be exacerbated discrepant pixel size relative to the MRI slice thickness. This could explain why no correlation was found between MRI and histological parameters. MRI may be best reserved for assessing fistula intensity, which was lowest following fibrin sealant treatment. While decreased MRI track intensity has previously been reported (Chan et al., 2002) following sealant treatment, there was no measurable change in the intensity of fistulas treated by either sealant or seton over time in the present study.

Fibrin sealant was not evident in any track assessed histologically, even those sectioned only two weeks following sealant instillation. Sealants persist *in vivo* aided by the anti-fibrinolytic agent, aprotinin, however they can lose up to 50% of their volume only 12 hours after instillation, and in addition lose almost 50% of their fibrin content within 5 days. Fibrin sealants provide a tissue matrix which native cells can penetrate. This process, which ultimately produces collagen, can be impeded at several points. Persisting granulation tissue can act as a barrier and inhibit cellular migration. Sealant volume loss compounds this problem, as any migrating cells then have a diminished

surface area with which to make contact as the fibrin clot contracts. Furthermore, in the present study, a foreign body type giant cell reaction was present in some of the tracks treated by sealant. This might represent sealant rejection. These factors could provide an explanation for the failure of sealant in the clinical setting (chapter 10).

In the future, tissue products with enhanced volume retention, particularly where these contain autologous cultured fibroblasts, could potentially render the stage of cellular migration unnecessary, and might, facilitate an improved outcome. To further optimise this treatment, longstanding granulation tissue and with it any areas of epithelialization ought to be removed to provide a clean, well-vascularised tissue bed, from which new granulation tissue might invade sealant or other tissue product applied.

In summary, a porcine model of anal fistula is feasible. Histological assessment of fistula tracks shows a large volume of granulation tissue, which is still present, albeit diminished, following curettage combined with seton or sealant therapy. Complete removal of all longstanding, possibly epithelialized, granulation tissue coupled with the development of more durable tissue sealants may be important to ensure the future success of these sphincter preserving techniques.

Thesis Summary

This thesis has studied the pre-operative assessment of fistula-in-ano, the effect of preoperative imaging on surgical approach as well as outcome, aspects of sphincter conserving fistula surgery, and novel approaches to treatment.

The prospective study assessing the therapeutic impact of MRI and its effect on outcome (chapter 3) has shown a considerable benefit when MRI guided surgery is employed in patients with recurrent disease: this strategy reduces further relapse by up to 75%. Furthermore, surgeons failing to act on the additional information provided by imaging had significantly higher relapse rates when their patients were compared to those who always acted on these findings (57% vs. 16%). In this difficult group of patients, preoperative MRI should be mandatory prior to undertaking further surgery.

MRI also influenced surgery in those patients presenting with primary fistula in 10% of cases (chapter 4). The two patients in this study believed to have a sinus at EUA, but found to have a fistula following MRI disclosure, would likely have recurred in the absence of imaging (chapter 3). While the therapeutic impact is less than in patients with recurrent disease, it could be argued that MRI should be performed in all patients with primary fistula-in-ano in return for a therapeutic impact of 10%.

Whilst AES might represent a cheaper alternative, MRI remains the most accurate pre-operative tool for fistula assessment (chapter 5), AES is intermediate and digital examination fared worst in all comparisons made. However, categorical agreement for AES was generally 'good,' with 91% of internal openings correctly identified, a figure approaching the 97% achieved by MRI. AES is well suited to answering this question both rapidly and inexpensively, and might be the imaging modality of choice in primary

fistula-in-ano, with MRI reserved for recurrent disease as it most accurately detected extensions. This hypothesis deserves further study.

Three-dimensional studies enabled blinded endosonographic comparisons, and found that hydrogen peroxide instillation did not improve fistula or extension detection (chapter 6). This may be because un-enhanced 3D-EAUS was 95% correct in localising internal openings in the anal canal, which was assisted by the multi-planar properties of 3D-EAUS enabling the plane of the track to be visualised. However, gas tracked down to the internal opening in only 44%, so this sign cannot be relied upon for diagnosis. Exudate or debris impeding track patency might also explain why only 32% of fistulas and 46% of secondary tracks filled completely with gas. In essence, this technique, which makes some tracks more conspicuous, is probably only useful in difficult cases.

Unsurprisingly, an expert observer was most accurate when using MRI for pre-operative assessment (chapter 7). However, this was rectified by a period of directed education, suggesting that the technique may be mastered rapidly given the right training environment.

In chapter 8, the angular relationship of trans-sphincteric fistulas relative to the longitudinal axis of the anal canal was measured using body-coil MRI. It had previously been suggested that internal opening height does not always reflect the level at which trans-sphincteric fistulas cross the external anal sphincter (Thomson & Parks, 1979), and the present study showed that half of trans-sphincteric fistulas tracked cranially and laterally through the sphincter complex, especially from internal openings above the dentate line, albeit that many of these cases were tertiary referrals from other

institutions. This has important implications for fistulotomy, which would divide more sphincter muscle than would ordinarily be appreciated from the palpable level of the internal opening, which might in turn precipitate faecal incontinence. Furthermore, these tracks might be difficult to probe and inexperienced probing might lead to iatrogenic track formation (Finlay, 1996). This important group of trans-sphincteric fistulas deserves careful attention.

The long-term results of the loose-seton technique (chapter 9), an alternative form of external sphincter preservation, were disappointing when compared with those obtained at short-term follow-up. However, this is important information, as patients can be adequately treated by loose-seton placement and may be happy with this option versus the consequences of recurrent sepsis in the long-term after seton removal. This study reflects the importance of long-term assessment of surgical techniques, and enables adequate counselling before seton removal.

Whilst fibrin sealant instillation has been proposed as a novel sphincter conserving treatment, the study presented in Chapter 10 reports a 14 percent success in the medium-term for complex anorectal fistulas without extension, despite seton placement to promote fibrosis, and adequate curettage. Patients studied included those in whom surgeons would not ordinarily perform fistulotomy. Previous studies assessing sphincter-preserving treatments for anal fistula, including surgical advancement flap, have used skin healing as a surrogate for fistula healing. This study emphasizes that a fistula has only healed when all openings and tracks have been eradicated, and MRI, which acted as a noninvasive tool to monitor fistula healing beneath the skin best predicted outcome in those with skin healing. Indeed, investigators have recently started

to incorporate MRI findings into their assessments of novel fistula treatments, such as the use of Infliximab (Bell et al., 2003a; Van Assche et al. 2003). The reasons for sealant failure are unclear, however fistula curettage was thought unlikely to remove all longstanding epithelialised granulation tissue. In this case a poorly prepared track could persist, thus failing to provide the correct environment for sealant to act as a matrix for cellular ingrowth.

Failure of sealant was further explored using an experimental porcine model in Chapter 11. This model provided similar anal canal musculature and glandular anatomy to humans. Furthermore, fistula-in-ano were easy to create and well tolerated, and the majority cultured enteric organisms.

The fistula lumen disappeared histologically, following treatment with curettage after seton removal both with and without sealant treatment. However, volumes of granulation tissue and MRI fistula intensity were consistently lower in tracks treated by sealant suggesting a beneficial effect for this technique. Whilst it has previously been suggested that curettage using a Volkmann's spoon might remove all granulation tissue (Cintron et al., 1999), this present study has demonstrated a large volume of granulation tissue relative to the fistula lumen volume. It would seem logical that recurrence is due to retained granulation tissue, as its original diameter may be up to 7mm. Core-out fistulectomy would seem appropriate to ensure complete healing after sealant instillation. In the future, tissue products with enhanced volume retention might further optimise this treatment, and further work in this area is required.

Conclusions

In conclusion, this thesis has demonstrated: -

- An important role for MRI-guided surgery in recurrent fistula-in-ano.
- A smaller role for MRI in primary fistula: further studies might concentrate on the potential benefits of using AES in these patients.
- Directed education is necessary before MR interpretation is performed in day-to-day clinical practice.
- Hydrogen peroxide enhancement during AES is probably of little benefit, especially when using 3D-AES.
- An important group of trans-sphincteric fistula, which need careful evaluation, almost certainly by a surgeon experienced in complex fistula.
- The medium and long-term outcome of simple sphincter conserving treatments including sealant and seton-removal is poor, however, as their prime aim is to preserve sphincter function, patients may be adequately counselled about success rates prior to undergoing treatment.
- An experimental model for fistula-in-ano is feasible.
- This model has suggested a role for core-out, and possibly more durable tissue products.

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Zimmerman DD, Briel JW & Schouten WR 2001b Endoanal advancement flap repair for complex anorectal fistulas. *Am.J.Surg.* **181**: 576-577.

Zimmerman DD, Delemarre JB, Gosselink MP, Hop WC, Briel JW & Schouten WR 2003 Smoking affects the outcome of transanal mucosal advancement flap repair of trans-sphincteric fistulas. *Br.J.Surg.* **90**: 351-354.

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APPENDIX

Publications arising from this Thesis

A. Original Articles

Buchanan GN, Halligan S, Williams AB, Cohen CRG, Tarroni D *et al.*
The effect of magnetic resonance imaging on clinical outcome in recurrent fistula-in-ano: a prospective trial
Lancet 2002; 360: 1661-2

Halligan S, Buchanan GN.
The effect of magnetic resonance imaging on clinical outcome in recurrent fistula-in-ano: a prospective trial (Letter)
Lancet 2003; 361: 1132-3

Buchanan GN, Halligan S, Williams AB, Cohen CRG, Tarroni D *et al.*
Magnetic Resonance Imaging For Primary Fistula-In-Ano: A Prospective Trial
British Journal of Surgery 2003; 90: 877-881

Buchanan GN, Bartram CI, Phillips RK, Gould S, Halligan S, Rockall T, Sibbons P, Cohen CRG.
The Efficacy Of Fibrin Sealant In The Management Of Complex Anal Fistula: A Prospective Trial
Diseases of the Colon and Rectum 2003; 46: 1167-1174

Buchanan GN, Williams A, Bartram CI, Halligan S, Nicholls RJ, Cohen CRG: The direction of the trans-sphincteric fistula track through the sphincter complex: its potential clinical significance
British Journal of Surgery 2003; 90: 1250-1255

Buchanan GN, Owen H, Torkington J, Lunniss PJ, Nicholls RJ, Cohen CRG. Long-term outcome following the loose seton technique for external sphincter preservation in complex anal fistula
British Journal of Surgery 2004; 91: 476-480

Buchanan GN, Halligan S, Taylor SA, Williams AB, Cohen CRG, Bartram CI.
Magnetic resonance imaging of fistula-in-ano: Inter- and Intra-observer agreement and effects of directed education
American Journal of Roentgenology 2004; 183: 135-40

Buchanan GN, Halligan S, Bartram CI, Williams AB, Tarroni D, Cohen CRG.
A prospective evaluation of clinical examination, endosonography, and magnetic resonance imaging for preoperative assessment of fistula-in-ano: Comparison to an outcome based reference standard.
Radiology (in press)

Buchanan GN, Bartram CI, Williams AB, Halligan S, Cohen CRG.
The value of hydrogen peroxide enhancement of three dimensional endoanal ultrasound in fistula-in-ano
Diseases of the Colon and Rectum (in press)

Buchanan GN, Sibbons P, Osborn M, Bartram CI, Ansari T, Halligan S, Cohen CRG.
Experimental Model Of Fistula-in-ano
Diseases of the Colon and Rectum (in press)

Buchanan GN, Sibbons P, Osborn M, Bartram CI, Ansari T, Halligan S, Cohen CRG.
Fibrin Sealant in Anal Fistula Model
Diseases of the Colon and Rectum (in press)

B. Abstracts

Buchanan GN Williams AB, Cohen CRG, Bartram CI, Phillips R *et al.*
The therapeutic impact of MRI in surgery for fistula-in-ano
Colorectal Disease 2002; 4:147-9

Buchanan GN, Halligan S, Williams A, Cohen CRG, Tarroni D, Phillips R, Bartram CI.
MRI for fistula-in-ano: Therapeutic impact and effect on outcome.
Colorectal Disease 2002; 4:(1) 35

Buchanan GN, Halligan S, Williams A, Cohen CRG, Bartram CI.
The effect of MRI on clinical outcome in recurrent fistula-in-ano: A Prospective Trial.
Diseases of the Colon and Rectum 2002; 45: A25-A28

Buchanan GN, Williams AB, Bartram CI, Halligan S, Nicholls RJ, Cohen CRG.
Angulation of trans-sphincteric fistula-in-ano through the sphincter complex: potential clinical significance.
Colorectal Disease 2003; 5: 381

Buchanan GN, Williams AB, Bartram CI, Halligan S, Nicholls RJ, Cohen CRG.
The anatomical relationship of the trans-sphincteric fistula-*in-ano* to the anal canal defined by magnetic resonance imaging
British Journal of Surgery 2003; 90: 598-638

Buchanan GN, Halligan S, Bartram CI, Williams AB, Cohen CRG.
Anal endosonography and clinical evaluation of fistula-in-ano: Prospective comparison with outcome derived gold standard
Colorectal Disease 2003; 5:384

Buchanan GN, Halligan S, Bartram CI, Williams AB, Cohen CRG.
Anal endosonography and clinical evaluation of fistula-*in-ano*: prospective comparison with outcome derived gold standard
British Journal of Surgery 2003; 90(S1): 79

Buchanan GN, Bartram CI, Phillips RKS, Gould S, Halligan S, Rockall T, Sibbons P, Cohen CRG
The efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial.
British Journal of Surgery 2003; 90(S1): 80

Buchanan GN, Williams AB, Bartram CI, Halligan S, Nicholls RJ, Cohen CRG.
The direction of the trans-sphincteric fistula track through the sphincter complex: its potential clinical significance
British Journal of Surgery 2003; 90(S1): 135

Buchanan GN, Williams AB, Bartram CI, Halligan S, Nicholls RJ, Cohen CRG.
The direction of the trans-sphincteric fistula track through the sphincter complex: its potential clinical significance.
Colorectal Disease 2003; 5(S1): 35-80

Buchanan GN, Halligan S, Bartram CI, Williams AB, Cohen CRG.
Anal endosonography and clinical evaluation of fistula-*in-ano*: prospective comparison with outcome derived gold standard
Colorectal Disease 2003; 5(S1): 35-80

Buchanan GN, Bartram CI, Phillips RKS, Gould S, Halligan S, Rockall T, Sibbons P, Cohen CRG
The efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial.
Colorectal Disease 2003; 5(S1): 35-80

Buchanan GN, Owen H, Torkington J, Bartram CI, Lunniss PJ, Halligan S, Phillips RK, Cohen CRG.
Long-term outcome following the loose-seton technique for external sphincter preservation in complex anal fistula
Colorectal Disease 2003; 5(S2): 1-4

C. Personal Presentations

October 2001: St. Mark's Hospital Association Annual Meeting
St. Mark's Hospital, London
MRI in surgery for fistula-in-ano

November 2001: Section of Coloproctology, Royal Society of Medicine
Royal Society of Medicine, London
The therapeutic impact of MRI in surgery for fistula-in-ano

November 2001: St Mark's Hospital Grand Round
St. Mark's Hospital, London
Imaging and Sphincter preservation in surgery for anal fistula

February 2002: SouthEast Thames Surgical Society
Maidstone Hospital, Kent
The effect of MRI on the outcome of anal fistula surgery

July 2002: Association of Coloproctology of Great Britain and Ireland Annual Meeting
Manchester, UK
MRI for fistula-in-ano: Therapeutic impact and effect on outcome.

October 2002: Meeting for Sir Alan Parks Visiting Professor, St Mark's Hospital
St. Mark's Hospital, London
Clinical implications of imaging anal fistula

October 2002: Tripartite Colorectal Meeting
Melbourne, Australia.
The effect of MRI on Clinical Outcome in Recurrent Fistula-in-ano: A Prospective Trial.

November 2002: Section of Coloproctology, Royal Society of Medicine
Royal Society of Medicine, London
The direction of the trans-sphincteric fistula track through the sphincter complex: its potential clinical significance.

January 2003: 3rd Meeting of the Society of Academic and Research Surgery
Leeds, UK
Direction of the trans-sphincteric fistula-in-ano: potential clinical significance.
(Poster)

February 2003: Section of Coloproctology, Royal Society of Medicine
Royal Society of Medicine, London
Anal endosonography and clinical evaluation of fistula-in-ano: prospective comparison with outcome derived gold standard

April 2003: Dartford Surgical Society
Dartford, UK
Anal fistula: evaluation and management.

May 2003: Association of Surgeons of Great Britain and Ireland Annual Meeting
Manchester, UK
The efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial.

May 2003: Association of Surgeons of Great Britain and Ireland Annual Meeting
Manchester, UK
Anal endosonography and clinical evaluation of fistula-in-ano: prospective comparison with outcome derived gold standard

May 2003: Association of Surgeons of Great Britain and Ireland Annual Meeting
Manchester, UK
Direction of the trans-sphincteric fistula-in-ano: potential clinical significance.
(Poster)

June 2003: American Society of Colon and Rectal Surgeons Annual Meeting
New Orleans, USA
The efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial. (Poster)

July 2003: Association of Coloproctology of Great Britain and Ireland Annual Meeting
Edinburgh, UK
Anal endosonography and clinical evaluation of fistula-in-ano: prospective comparison with outcome derived gold standard (Poster)

July 2003: Association of Coloproctology of Great Britain and Ireland Annual Meeting
Edinburgh, UK
Direction of the trans-sphincteric fistula-in-ano: potential clinical significance.
(Poster)

July 2003: Association of Coloproctology of Great Britain and Ireland Annual Meeting

Edinburgh, UK

The efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial.

September 2003: St Mark's Hospital Grand Round

St. Mark's Hospital, London

Improving the assessment and management of fistula-in-ano.

September 2003: European Association of Coloproctology Annual Meeting

Sitges, Barcelona, Spain

Long-term outcome following the loose-seton technique for external sphincter preservation in complex anal fistula

October 2003: Association of Coloproctology of Great Britain and Ireland, South East

Thames Chapter Annual Meeting

Haywards Heath, UK

The implications of anal fistula imaging for the colorectal surgeon

November 2003: European Gastroenterology Week

Madrid, Spain

Anatomical diagnosis of Crohn's fistula-in-ano: MRI and endosonography